Dossier zur Nutzenbewertung gemäß § 35a SGB V

Retardiertes Cacifediol (Rayaldee®)

Fresenius Medical Care Nephrologica Deutschland GmbH

Separater Anhang 4-H

Sekundärer Hyperparathyreoidismus bei Erwachsenen mit chronischer Nierenerkrankung im Stadium 3 oder 4 und Vitamin D-Mangel

Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen

Stand: 01.02.2022

Nachberechnungen für die Wirksamkeits- und Sicherheitsendpunkte der Studien CL-3001 und CL-3002 sowie für die Meta-Analyse

Fresenius Medical Care Nephrologica Deutschland GmbH (2021)

Nachberechnungsdokument

Wirksamkeitsendpunkte (ITT-Population)

Folgende Daten werden für die ITT-Population dargestellt:

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 ng/ml im Serum

Table 12.2.2.1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	141/141	72/72	144/144	72/72	285/285	144/144
Mean (SD)	146.8 (56.01)	142.2 (46.11)	147.6 (64.21)	155.6 (63.09)	147.2 (60.19)	148.9 (55.47)
Visit 5						
n/N	137/141	69/72	138/144	70/72	275/285	139/144
Mean (SD)	134.7 (61.08)	137.8 (56.26)	134.0 (73.95)	152.6 (69.52)	134.3 (67.72)	145.3 (63.49)
Visit 6						
n/N	134/141	67/72	134/144	69/72	268/285	136/144
Mean (SD)	126.0 (52.29)	147.3 (68.82)	128.7 (76.76)	160.7 (72.81)	127.4 (65.56)	154.1 (70.93)
Visit 7						
n/N	123/141	63/72	123/144	60/72	246/285	123/144
Mean (SD)	120.9 (58.49)	146.3 (67.89)	123.9 (74.09)	163.0 (82.31)	122.4 (66.63)	154.4 (75.43)
Visit 8						
n/N	126/141	68/72	128/144	63/72	254/285	131/144
Mean (SD)	121.3 (56.23)	142.0 (66.39)	125.3 (71.64)	164.7 (121.01)	123.3 (64.36)	152.9 (96.87)
Visit 9						
n/N	122/141	63/72	124/144	61/72	246/285	124/144
Mean (SD)	118.2 (59.54)	144.5 (69.27)	113.7 (70.38)	163.3 (80.06)	116.0 (65.14)	153.8 (75.06)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.2.2.1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Visit 10						
n/N	115/141	63/72	125/144	60/72	240/285	123/144
Mean (SD)	109.3 (52.30)	145.8 (71.57)	110.0 (64.01)	154.3 (83.07)	109.7 (58.57)	149.9 (77.19)
Visit 11						
n/N	109/141	59/72	112/144	57/72	221/285	116/144
Mean (SD)	107.7 (52.63)	148.5 (82.38)	120.9 (88.92)	146.5 (57.10)	114.4 (73.44)	147.5 (70.79)
Visit 12						
n/N	114/141	62/72	119/144	57/72	233/285	119/144
Mean (SD)	105.5 (51.45)	139.2 (64.09)	114.4 (86.45)	162.3 (77.47)	110.0 (71.49)	150.3 (71.46)
Visit 13/ET						
n/N	129/141	68/72	132/144	63/72	261/285	131/144
Mean (SD)	114.2 (61.85)	148.7 (65.32)	116.2 (90.60)	169.9 (83.30)	115.2 (77.59)	158.9 (74.98)
EAP						
n/N	117/141	64/72	124/144	61/72	241/285	125/144
Mean (SD)	109.6 (50.95)	146.1 (65.16)	113.1 (76.29)	157.0 (64.89)	111.4 (65.12)	151.4 (64.99)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.2.2.1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-32.7 (4.36)	7.8 (6.00)	-28.3 (5.17)	11.4 (7.50)	-31.0 (3.42)	10.6 (4.82)
95% CI	[-41.24, -24.06]	[-4.04, 19.65]	[-38.50, -18.10]	[-3.44, 26.15]	[-37.70, -24.27]	[1.12, 20.09]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.45		-39.66		-41.59	
95% CI	[-55.10, -25.81]		[-57.67, -21.64]		[-53.21, -29.96]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.9646	
Hedges' g	-0.83		-0.68		-0.75	
95% CI	[-1.13, -0.52]		[-0.98, -0.37]		[-0.96, -0.53]	
heterogeneity p-value					0.4874	
I^2					0.0%	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.4 (3.85)	7.3 (5.21)	-29.5 (4.18)	4.4 (5.97)	-32.2 (2.85)	6.2 (3.96)
95% CI	[-42.05, -26.84]	[-2.96, 17.62]	[-37.76, -21.25]	[-7.37, 16.19]	[-37.79, -26.56]	[-1.54, 14.04]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-41.77		-33.91		-38.42	
95% CI	[-54.58, -28.97]		[-48.32, -19.51]		[-48.02, -28.82]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.4233	
Hedges' g	-1.00		-0.71		-0.85	
95% CI	[-1.33, -0.68]		[-1.02, -0.39]		[-1.08, -0.63]	
heterogeneity p-value					0.1945	
I^2					40.6%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.2.1.1.1
Number (n, %) of Subjects with a Mean Reduction of >=30% in Plasma iPTH
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
EAP; n/N (%)	46/141 (32.6)	6/72 (8.3)	49/144 (34.0)	5/72 (6.9)	95/285 (33.3)	11/144 (7.6)
RR [95%-CI]; p-value	3.91 [1.76, 8.73], 0.0009		4.90 [2.04, 11.76], 0.0004		4.36 [2.42, 7.88], <0.0001	
OR [95%-CI]; p-value	5.33 [2.15, 13.19], <0.0001		6.91 [2.62, 18.27], <0.0001		6.05 [3.12, 11.72], <0.0001	
RD [95%-CI]; p-value	0.24 [0.14, 0.34], <0.0001		0.27 [0.17, 0.37], <0.0001		0.26 [0.19, 0.33], <0.0001	
heterogeneity (RR)						
p-value					0.7110	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.7005	
Visit 13/ET; n/N (%)	54/141 (38.3)	7/72 (9.7)	61/144 (42.4)	8/72 (11.1)	115/285 (40.4)	15/144 (10.4)
RR [95%-CI]; p-value	3.94 [1.89, 8.21], 0.0003		3.81 [1.93, 7.53], 0.0001		3.87 [2.35, 6.38], <0.0001	
OR [95%-CI]; p-value	5.76 [2.46, 13.49], <0.0001		5.88 [2.63, 13.16], <0.0001		5.82 [3.24, 10.44], <0.0001	
RD [95%-CI]; p-value	0.29 [0.18, 0.39], <0.0001		0.31 [0.20, 0.42], <0.0001		0.30 [0.22, 0.38], <0.0001	
heterogeneity (RR)						
p-value					0.9490	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9734	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1

Table 12.2.1.1.2
Number (n, %) of Subjects with a Mean Reduction of >=10% in Plasma iPTH
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
EAP; n/N (%)	87/141 (61.7)	17/72 (23.6)	90/144 (62.5)	18/72 (25.0)	177/285 (62.1)	35/144 (24.3)
RR [95%-CI]; p-value	2.61 [1.69, 4.04], <0.0001		2.50 [1.64, 3.80], <0.0001		2.56 [1.89, 3.46], <0.0001	
OR [95%-CI]; p-value	5.21 [2.75, 9.90], <0.0001		5.00 [2.66, 9.40], <0.0001		5.10 [3.26, 8.00], <0.0001	
RD [95%-CI]; p-value	0.38 [0.25, 0.51], <0.0001		0.38 [0.25, 0.50], <0.0001		0.38 [0.29, 0.47], <0.0001	
heterogeneity (RR)						
p-value					0.8858	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9278	
Visit 13/ET; n/N (%)	90/141 (63.8)	19/72 (26.4)	96/144 (66.7)	20/72 (27.8)	186/285 (65.3)	39/144 (27.1)
RR [95%-CI]; p-value	2.42 [1.61, 3.63], <0.0001		2.40 [1.63, 3.54], <0.0001		2.41 [1.82, 3.19], <0.0001	
OR [95%-CI]; p-value	4.92 [2.63, 9.21], <0.0001		5.20 [2.79, 9.68], <0.0001		5.06 [3.25, 7.86], <0.0001	
RD [95%-CI]; p-value	0.37 [0.25, 0.50], <0.0001		0.39 [0.26, 0.52], <0.0001		0.38 [0.29, 0.47], <0.0001	
heterogeneity (RR)						
p-value					0.9783	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9031	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1

Table 12.3.2.1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	141/141	72/72	144/144	72/72	285/285	144/144
Mean (SD)	20.2 (5.08)	19.2 (5.43)	19.7 (5.56)	19.4 (5.51)	19.9 (5.32)	19.3 (5.46)
Visit 5						
n/N	137/141	68/72	138/144	70/72	275/285	138/144
Mean (SD)	34.1 (10.34)	18.8 (5.72)	34.4 (11.55)	18.4 (6.18)	34.2 (10.94)	18.6 (5.94)
Visit 6						
n/N	135/141	68/72	133/144	68/72	268/285	136/144
Mean (SD)	41.3 (12.64)	19.1 (6.85)	42.0 (15.01)	19.8 (8.75)	41.6 (13.85)	19.5 (7.83)
Visit 7						
n/N	123/141	64/72	122/144	60/72	245/285	124/144
Mean (SD)	42.9 (12.65)	17.9 (5.69)	45.0 (15.47)	18.6 (6.28)	44.0 (14.14)	18.2 (5.97)
Visit 8						
n/N	127/141	68/72	129/144	63/72	256/285	131/144
Mean (SD)	45.8 (14.60)	18.0 (6.30)	47.4 (16.56)	18.6 (6.01)	46.6 (15.61)	18.3 (6.15)
Visit 9						
n/N	122/141	64/72	124/144	63/72	246/285	127/144
Mean (SD)	57.8 (18.19)	17.6 (6.54)	58.3 (22.00)	18.7 (6.90)	58.0 (20.16)	18.1 (6.71)

Abbreviations: 25 D: 25-Hydroxyvitamin D; SD: Standard Deviation; ET: End of Treatment; EAP: Efficacy Assessment Phase; ER: Extended Release; ITT: Intention-To-Treat; LS: Least Square; Diff: Difference; CI: Confidence Interval; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.3.2.1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Visit 10						
n/N	117/141	64/72	124/144	61/72	241/285	125/144
Mean (SD)	65.2 (23.29)	17.6 (6.59)	64.8 (22.07)	19.3 (6.86)	65.0 (22.62)	18.4 (6.75)
Visit 11						
n/N	110/141	59/72	114/144	58/72	224/285	117/144
Mean (SD)	66.6 (22.56)	17.8 (6.60)	66.6 (22.73)	19.6 (7.37)	66.6 (22.60)	18.7 (7.02)
Visit 12						
n/N	114/141	60/72	122/144	59/72	236/285	119/144
Mean (SD)	68.9 (24.79)	18.1 (6.99)	66.9 (23.48)	19.4 (6.68)	67.9 (24.09)	18.7 (6.84)
Visit 13/ET						
n/N	131/141	68/72	132/144	62/72	263/285	130/144
Mean (SD)	65.1 (24.62)	17.5 (6.18)	65.7 (24.57)	19.9 (6.72)	65.4 (24.55)	18.6 (6.53)
EAP						
n/N	118/141	64/72	124/144	61/72	242/285	125/144
Mean (SD)	67.0 (22.25)	17.6 (6.25)	66.8 (21.41)	19.4 (6.51)	66.9 (21.78)	18.5 (6.42)

Abbreviations: 25 D: 25-Hydroxyvitamin D; SD: Standard Deviation; ET: End of Treatment; EAP: Efficacy Assessment Phase; ER: Extended Release; ITT: Intention-To-Treat; LS: Least Square; Diff: Difference; CI: Confidence Interval; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
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Table 12.3.2.1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.1 (1.74)	-1.8 (2.41)	46.0 (1.76)	0.1 (2.56)	45.6 (1.23)	-0.9 (1.76)
95% CI	[41.63, 48.48]	[-6.57, 2.95]	[42.58, 49.51]	[-4.99, 5.12]	[43.13, 47.98]	[-4.33, 2.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.87		45.98		46.43	
95% CI	[41.00, 52.74]		[39.85, 52.11]		[42.21, 50.65]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.8340	
Hedges' g	2.35		2.27		2.32	
95% CI	[1.98, 2.72]		[1.90, 2.65]		[2.06, 2.59]	
heterogeneity p-value					0.7827	
I^2					0.0%	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.2 (1.63)	-1.7 (2.22)	47.1 (1.55)	0.1 (2.21)	47.2 (1.12)	-0.8 (1.56)
95% CI	[43.99, 50.43]	[-6.03, 2.72]	[44.06, 50.17]	[-4.27, 4.44]	[44.95, 49.37]	[-3.86, 2.29]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.87		47.03		47.95	
95% CI	[43.42, 54.31]		[41.71, 52.35]		[44.16, 51.73]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.6352	
Hedges' g	2.75		2.72		2.75	
95% CI	[2.33, 3.16]		[2.31, 3.13]		[2.45, 3.04]	
heterogeneity p-value					0.9314	
I^2					0.0%	

Abbreviations: 25 D: 25-Hydroxyvitamin D; SD: Standard Deviation; ET: End of Treatment; EAP: Efficacy Assessment Phase; ER: Extended Release; ITT: Intention-To-Treat; LS: Least Square; Diff: Difference; CI: Confidence Interval; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

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Table 12.3.1.1
Number (n, %) of Subjects with Adequate Serum 25D Levels (>=30 ng/mL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
EAP; n/N (%)	113/141 (80.1)	2/72 (2.8)	120/144 (83.3)	5/72 (6.9)	233/285 (81.8)	7/144 (4.9)
RR [95%-CI]; p-value	28.85 [7.34, 113.42], <0.0001		12.00 [5.14, 28.04], <0.0001		16.82 [8.15, 34.71], <0.0001	
OR [95%-CI]; p-value	141.25 [32.63, 611.38], <0.0001		67.00 [24.43, 183.74], <0.0001		87.70 [38.75, 198.48], <0.0001	
RD [95%-CI]; p-value	0.77 [0.70, 0.85], <0.0001		0.76 [0.68, 0.85], <0.0001		0.77 [0.71, 0.83], <0.0001	
heterogeneity (RR)						
p-value					0.2858	
I^2					12.2%	
heterogeneity (OR)						
p-value					0.4009	
Visit 13/ET; n/N (%)	117/141 (83.0)	2/72 (2.8)	123/144 (85.4)	6/72 (8.3)	240/285 (84.2)	8/144 (5.6)
RR [95%-CI]; p-value	29.87 [7.60, 117.39], <0.0001		10.25 [4.75, 22.12], <0.0001		15.16 [7.72, 29.78], <0.0001	
OR [95%-CI]; p-value	170.63 [39.13, 744.01], <0.0001		64.43 [24.79, 167.48], <0.0001		90.67 [41.52, 197.96], <0.0001	
RD [95%-CI]; p-value	0.80 [0.73, 0.87], <0.0001		0.77 [0.68, 0.86], <0.0001		0.79 [0.73, 0.84], <0.0001	
heterogeneity (RR)						
p-value					0.1817	
I^2					43.9%	
heterogeneity (OR)						
p-value					0.2633	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1

Nachberechnungsdokument

Wirksamkeitsendpunkte (PP-Population)

Folgende Daten werden für die PP-Population dargestellt:

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit eine 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

Table 12.2.2.1.s10
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	144.4 (51.85)	136.9 (41.35)	142.9 (62.34)	153.9 (58.85)	143.7 (57.31)	145.3 (51.22)
Visit 5						
n/N	115/115	61/62	118/119	59/60	233/234	120/122
Mean (SD)	134.1 (59.04)	133.5 (55.73)	128.4 (69.50)	152.6 (66.55)	131.2 (64.47)	142.9 (61.78)
Visit 6						
n/N	115/115	61/62	119/119	60/60	234/234	121/122
Mean (SD)	126.8 (50.93)	142.3 (68.06)	124.7 (72.23)	160.6 (75.77)	125.8 (62.55)	151.3 (72.27)
Visit 7						
n/N	106/115	57/62	112/119	52/60	218/234	109/122
Mean (SD)	123.8 (57.75)	142.4 (68.51)	122.9 (72.21)	167.3 (86.44)	123.3 (65.43)	154.3 (78.22)
Visit 8						
n/N	114/115	62/62	117/119	58/60	231/234	120/122
Mean (SD)	122.9 (55.43)	140.5 (69.10)	122.5 (68.18)	169.1 (124.82)	122.7 (62.08)	154.3 (100.58)
Visit 9						
n/N	113/115	60/62	116/119	58/60	229/234	118/122
Mean (SD)	120.9 (59.84)	144.3 (70.60)	113.8 (71.80)	162.8 (79.19)	117.3 (66.12)	153.4 (75.20)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.2.2.1.s10
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Visit 10						
n/N	113/115	61/62	118/119	59/60	231/234	120/122
Mean (SD)	109.3 (52.73)	145.7 (72.49)	110.1 (65.40)	155.4 (83.31)	109.7 (59.42)	150.5 (77.82)
Visit 11						
n/N	107/115	57/62	107/119	56/60	214/234	113/122
Mean (SD)	107.4 (53.09)	148.4 (83.07)	121.9 (90.53)	148.1 (56.29)	114.7 (74.39)	148.2 (70.75)
Visit 12						
n/N	112/115	60/62	115/119	57/60	227/234	117/122
Mean (SD)	105.0 (51.70)	139.8 (64.99)	115.6 (87.49)	162.3 (77.47)	110.4 (72.12)	150.8 (71.93)
Visit 13/ET						
n/N	114/115	61/62	117/119	58/60	231/234	119/122
Mean (SD)	113.3 (61.73)	148.7 (66.67)	110.9 (88.38)	166.4 (75.88)	112.1 (76.24)	157.3 (71.55)
EAP						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	109.5 (51.39)	146.5 (66.16)	114.0 (77.62)	158.2 (64.81)	111.8 (65.94)	152.3 (65.49)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.2.2.1.s10
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.5 (4.67)	12.4 (6.39)	-32.4 (5.50)	12.4 (7.82)	-31.7 (3.61)	12.9 (5.03)
95% CI	[-39.76, -21.33]	[-0.20, 25.03]	[-43.23, -21.53]	[-3.04, 27.83]	[-38.82, -24.62]	[3.00, 22.79]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-42.96		-44.77		-44.61	
95% CI	[-58.61, -27.31]		[-63.67, -25.88]		[-56.79, -32.43]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.8985	
Hedges' g	-0.88		-0.75		-0.81	
95% CI	[-1.20, -0.56]		[-1.07, -0.42]		[-1.04, -0.58]	
heterogeneity p-value					0.5665	
I^2					0.0%	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.5 (3.87)	8.7 (5.28)	-29.2 (4.33)	4.8 (6.10)	-32.0 (2.91)	7.1 (4.03)
95% CI	[-42.11, -26.82]	[-1.74, 19.11]	[-37.74, -20.65]	[-7.22, 16.87]	[-37.73, -26.29]	[-0.83, 15.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.15		-34.02		-39.10	
95% CI	[-56.09, -30.20]		[-48.81, -19.23]		[-48.88, -29.33]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.3581	
Hedges' g	-1.05		-0.70		-0.86	
95% CI	[-1.37, -0.72]		[-1.02, -0.38]		[-1.09, -0.64]	
heterogeneity p-value					0.1352	
I^2					55.2%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/T12_2_2_1_m_pth_pp.sas using SAS 9.4

Table 12.2.1.1.1.s10
Number (n, %) of Subjects with a Mean Reduction of >=30% in Plasma iPTH
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
EAP; n/N (%)	46/115 (40.0)	5/62 (8.1)	47/119 (39.5)	5/60 (8.3)	93/234 (39.7)	10/122 (8.2)
RR [95%-CI]; p-value	4.96 [2.08, 11.84], 0.0003		4.74 [1.99, 11.29], 0.0004		4.85 [2.62, 8.96], <0.0001	
OR [95%-CI]; p-value	7.60 [2.83, 20.40], <0.0001		7.18 [2.68, 19.26], <0.0001		7.39 [3.68, 14.84], <0.0001	
RD [95%-CI]; p-value	0.32 [0.21, 0.43], <0.0001		0.31 [0.20, 0.42], <0.0001		0.32 [0.24, 0.39], <0.0001	
heterogeneity (RR)						
p-value					0.9422	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9365	
Visit 13/ET; n/N (%)	49/115 (42.6)	6/62 (9.7)	58/119 (48.7)	7/60 (11.7)	107/234 (45.7)	13/122 (10.7)
RR [95%-CI]; p-value	4.40 [2.00, 9.70], 0.0002		4.18 [2.03, 8.58], <0.0001		4.29 [2.52, 7.31], <0.0001	
OR [95%-CI]; p-value	6.93 [2.76, 17.38], <0.0001		7.20 [3.03, 17.12], <0.0001		7.06 [3.76, 13.26], <0.0001	
RD [95%-CI]; p-value	0.33 [0.21, 0.45], <0.0001		0.37 [0.25, 0.49], <0.0001		0.35 [0.27, 0.43], <0.0001	
heterogeneity (RR)						
p-value					0.9233	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9527	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1

Table 12.2.1.1.2.s10
Number (n, %) of Subjects with a Mean Reduction of >=10% in Plasma iPTH
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
EAP; n/N (%)	85/115 (73.9)	16/62 (25.8)	85/119 (71.4)	17/60 (28.3)	170/234 (72.6)	33/122 (27.0)
RR [95%-CI]; p-value	2.86 [1.85, 4.43], <0.0001		2.52 [1.66, 3.83], <0.0001		2.69 [1.99, 3.63], <0.0001	
OR [95%-CI]; p-value	8.15 [4.03, 16.48], <0.0001		6.32 [3.18, 12.58], <0.0001		7.16 [4.38, 11.72], <0.0001	
RD [95%-CI]; p-value	0.48 [0.35, 0.62], <0.0001		0.43 [0.29, 0.57], <0.0001		0.46 [0.36, 0.55], <0.0001	
heterogeneity (RR)						
p-value					0.6788	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6143	
Visit 13/ET; n/N (%)	78/115 (67.8)	15/62 (24.2)	87/119 (73.1)	18/60 (30.0)	165/234 (70.5)	33/122 (27.0)
RR [95%-CI]; p-value	2.80 [1.77, 4.43], <0.0001		2.44 [1.63, 3.64], <0.0001		2.61 [1.93, 3.53], <0.0001	
OR [95%-CI]; p-value	6.61 [3.28, 13.31], <0.0001		6.34 [3.20, 12.58], <0.0001		6.45 [3.96, 10.51], <0.0001	
RD [95%-CI]; p-value	0.44 [0.30, 0.57], <0.0001		0.43 [0.29, 0.57], <0.0001		0.43 [0.34, 0.53], <0.0001	
heterogeneity (RR)						
p-value					0.6522	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9355	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1

Table 12.3.2.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	19.8 (5.13)	19.3 (5.67)	19.6 (5.55)	19.3 (5.63)	19.7 (5.34)	19.3 (5.63)
Visit 5						
n/N	114/115	60/62	118/119	60/60	232/234	120/122
Mean (SD)	33.3 (10.41)	19.0 (5.80)	34.9 (11.78)	18.4 (6.43)	34.1 (11.13)	18.7 (6.10)
Visit 6						
n/N	115/115	62/62	118/119	59/60	233/234	121/122
Mean (SD)	40.7 (12.39)	19.3 (6.91)	43.2 (15.04)	19.7 (8.94)	42.0 (13.83)	19.5 (7.93)
Visit 7						
n/N	106/115	58/62	111/119	52/60	217/234	110/122
Mean (SD)	42.4 (12.46)	18.0 (5.68)	45.5 (15.86)	18.6 (6.18)	44.0 (14.35)	18.3 (5.90)
Visit 8						
n/N	115/115	62/62	118/119	58/60	233/234	120/122
Mean (SD)	45.5 (14.62)	18.2 (6.14)	48.2 (16.72)	18.8 (5.99)	46.9 (15.74)	18.5 (6.05)
Visit 9						
n/N	113/115	61/62	117/119	60/60	230/234	121/122
Mean (SD)	57.8 (18.11)	17.8 (6.62)	58.8 (21.90)	19.0 (6.84)	58.3 (20.09)	18.4 (6.73)

Abbreviations: 25 D: 25-Hydroxyvitamin D; SD: Standard Deviation; ET: End of Treatment; EAP: Efficacy Assessment Phase; ER: Extended Release; PP: Per-Protocol; LS: Least Square; Diff: Difference; CI: Confidence Interval; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.3.2.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Visit 10						
n/N	114/115	62/62	117/119	60/60	231/234	122/122
Mean (SD)	65.0 (23.59)	17.7 (6.59)	65.8 (21.56)	19.4 (6.88)	65.4 (22.54)	18.5 (6.76)
Visit 11						
n/N	108/115	57/62	109/119	57/60	217/234	114/122
Mean (SD)	66.4 (22.68)	17.9 (6.63)	67.1 (22.21)	19.6 (7.43)	66.7 (22.39)	18.7 (7.06)
Visit 12						
n/N	112/115	58/62	117/119	59/60	229/234	117/122
Mean (SD)	68.5 (24.84)	18.1 (7.04)	67.3 (22.76)	19.4 (6.68)	67.9 (23.76)	18.8 (6.86)
Visit 13/ET						
n/N	115/115	61/62	117/119	57/60	232/234	118/122
Mean (SD)	67.8 (23.86)	17.4 (6.32)	69.2 (22.59)	20.0 (6.92)	68.5 (23.19)	18.6 (6.72)
EAP						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	66.8 (22.48)	17.7 (6.27)	67.3 (20.90)	19.5 (6.54)	67.1 (21.65)	18.6 (6.44)

Abbreviations: 25 D: 25-Hydroxyvitamin D; SD: Standard Deviation; ET: End of Treatment; EAP: Efficacy Assessment Phase; ER: Extended Release; PP: Per-Protocol; LS: Least Square; Diff: Difference; CI: Confidence Interval; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/T12_3_2_1_m_25d_pp.sas using SAS 9.4

Table 12.3.2.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	47.9 (1.77)	-1.9 (2.43)	49.6 (1.72)	0.4 (2.46)	48.8 (1.23)	-0.8 (1.73)
95% CI	[44.43, 51.42]	[-6.68, 2.92]	[46.20, 52.98]	[-4.50, 5.22]	[46.35, 51.20]	[-4.19, 2.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.81		49.23		49.56	
95% CI	[43.87, 55.75]		[43.31, 55.16]		[45.38, 53.74]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.8777	
Hedges' g	2.62		2.64		2.64	
95% CI	[2.21, 3.03]		[2.22, 3.06]		[2.35, 2.94]	
heterogeneity p-value					0.9552	
I^2					0.0%	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (1.67)	-1.6 (2.28)	47.7 (1.54)	0.2 (2.17)	47.3 (1.13)	-0.7 (1.57)
95% CI	[43.69, 50.29]	[-6.07, 2.93]	[44.64, 50.72]	[-4.07, 4.49]	[45.10, 49.57]	[-3.77, 2.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.56		47.47		48.02	
95% CI	[42.98, 54.15]		[42.21, 52.72]		[44.20, 51.83]	
p-value	<0.0001		<0.0001		<0.0001	
heterogeneity p-value					0.7753	
Hedges' g	2.70		2.82		2.77	
95% CI	[2.28, 3.12]		[2.39, 3.24]		[2.47, 3.07]	
heterogeneity p-value					0.7029	
I^2					0.0%	

Abbreviations: 25 D: 25-Hydroxyvitamin D; SD: Standard Deviation; ET: End of Treatment; EAP: Efficacy Assessment Phase; ER: Extended Release; PP: Per-Protocol; LS: Least Square; Diff: Difference; CI: Confidence Interval; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/T12_3_2_1_m_25d_pp.sas using SAS 9.4

Table 12.3.1.1.s10
Number (n, %) of Subjects with Adequate Serum 25D Levels (>=30 ng/mL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
EAP; n/N (%)	110/115 (95.7)	2/62 (3.2)	116/119 (97.5)	5/60 (8.3)	226/234 (96.6)	7/122 (5.7)
RR [95%-CI]; p-value	29.65 [7.58, 115.98], <0.0001		11.70 [5.05, 27.09], <0.0001		16.83 [8.20, 34.57], <0.0001	
OR [95%-CI]; p-value	660.00 [124.28, 3505.05], <0.0001		425.33 [98.10, 1844.11], <0.0001		464.11 [164.22, 1311.65], <0.0001	
RD [95%-CI]; p-value	0.92 [0.87, 0.98], <0.0001		0.89 [0.82, 0.97], <0.0001		0.91 [0.86, 0.96], <0.0001	
heterogeneity (RR)						
p-value					0.2550	
I^2					22.8%	
heterogeneity (OR)						
p-value					0.6979	
Visit 13/ET; n/N (%)	104/115 (90.4)	2/62 (3.2)	115/119 (96.6)	6/60 (10.0)	219/234 (93.6)	8/122 (6.6)
RR [95%-CI]; p-value	28.03 [7.16, 109.74], <0.0001		9.66 [4.52, 20.66], <0.0001		14.27 [7.30, 27.91], <0.0001	
OR [95%-CI]; p-value	283.64 [60.82, 1322.75], <0.0001		258.75 [70.11, 954.97], <0.0001		208.05 [85.66, 505.32], <0.0001	
RD [95%-CI]; p-value	0.87 [0.80, 0.94], <0.0001		0.87 [0.78, 0.95], <0.0001		0.87 [0.82, 0.92], <0.0001	
heterogeneity (RR)						
p-value					0.1814	
I^2					44.0%	
heterogeneity (OR)						
p-value					0.9282	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1

Nachberechnungsdokument
Sicherheitsendpunkte
Sicherheits-relevante sHPT-assoziierte Parameter (ITT-Population)

Folgende Daten werden für die ITT-Population dargestellt:

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperkalzämie
- Anteil Patienten mit einer Hyperkalzurie

- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperphosphatämie

- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum

- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

Table 12.4.12.1
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	141/141	72/72	144/144	72/72	285/285	144/144
Mean (SD)	9.2 (0.29)	9.2 (0.28)	9.2 (0.35)	9.3 (0.28)	9.2 (0.32)	9.2 (0.28)
Visit 8						
n/N	126/141	68/72	128/144	63/72	254/285	131/144
Mean (SD)	9.3 (0.63)	9.3 (0.44)	9.4 (0.48)	9.3 (0.50)	9.4 (0.56)	9.3 (0.47)
Visit 13/ET						
n/N	131/141	68/72	132/144	62/72	263/285	130/144
Mean (SD)	9.5 (0.50)	9.3 (0.32)	9.5 (0.40)	9.4 (0.54)	9.5 (0.45)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.03)	0.1 (0.05)	0.3 (0.03)	0.1 (0.05)	0.3 (0.02)	0.1 (0.03)
95% CI	[0.23, 0.36]	[0.02, 0.21]	[0.22, 0.34]	[0.01, 0.19]	[0.24, 0.33]	[0.04, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.18		0.18	
95% CI	[0.06, 0.30]		[0.07, 0.29]		[0.10, 0.26]	
p-value	0.0025		0.0011		<0.0001	
heterogeneity p-value					0.9978	
Hedges' g	0.48		0.51		0.49	
95% CI	[0.18, 0.78]		[0.20, 0.81]		[0.28, 0.71]	
heterogeneity p-value					0.8962	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.19.1.2
Number (n, %) of Subjects with Hypercalcemia (two consecutive visits with serum Ca >10.3 mg/dL) Deemed to Be Study Drug Related
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
EAP						
n/N (%)	4/141 (2.8)	0/72 (0.0)	2/144 (1.4)	0/72 (0.0)	6/285 (2.1)	0/144 (0.0)
RR [95%-CI]; p-value	4.11 [0.22, 76.75], 0.3435		2.01 [0.09, 44.09], 0.6566		6.08 [0.34, 108.17], 0.2188	
OR [95%-CI]; p-value	4.20 [0.22, 80.63], 0.3010		2.03 [0.09, 45.56], 0.6495		6.19 [0.34, 111.66], 0.1582	
RD [95%-CI]; p-value	0.02 [-0.01, 0.05], 0.2073		0.01 [-0.02, 0.03], 0.6116		0.02 [-0.00, 0.04], 0.0728	
heterogeneity (RR)						
p-value					0.7420	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.7359	

Abbreviations: Ca: Calcium; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_19_1_2_m_hyperca.sas using SAS 9.4

Table 12.4.15.1.3
Number (n, %) of Subjects with Hypercalciuria (>200 mg calcium/g creatinine)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Visit 13/ET						
n/N (%)	3/141 (2.1)	1/72 (1.4)	4/144 (2.8)	1/72 (1.4)	7/285 (2.5)	2/144 (1.4)
RR [95%-CI]; p-value	1.53 [0.16, 14.47], 0.7097		2.00 [0.23, 17.57], 0.5318		1.77 [0.37, 8.40], 0.4735	
OR [95%-CI]; p-value	1.54 [0.16, 15.11], 0.7071		2.03 [0.22, 18.49], 0.5222		1.79 [0.37, 8.72], 0.4664	
RD [95%-CI]; p-value	0.01 [-0.03, 0.04], 0.6878		0.01 [-0.02, 0.05], 0.4749		0.01 [-0.02, 0.04], 0.4253	
heterogeneity (RR)						
p-value					0.8672	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8659	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_15_1_3_m_hyperuca.sas using SAS 9.4

Table 12.4.14.1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	141/141	72/72	144/144	72/72	285/285	144/144
Mean (SD)	3.7 (0.55)	3.8 (0.59)	3.8 (0.56)	3.7 (0.47)	3.7 (0.55)	3.8 (0.53)
Visit 5						
n/N	137/141	68/72	139/144	71/72	276/285	139/144
Mean (SD)	3.9 (0.69)	3.8 (0.67)	3.9 (0.64)	3.8 (0.72)	3.9 (0.66)	3.8 (0.69)
Visit 6						
n/N	134/141	68/72	132/144	69/72	266/285	137/144
Mean (SD)	3.8 (0.60)	3.9 (0.70)	4.0 (0.68)	3.9 (0.78)	3.9 (0.65)	3.9 (0.74)
Visit 7						
n/N	123/141	64/72	122/144	60/72	245/285	124/144
Mean (SD)	3.9 (0.63)	3.9 (0.69)	3.9 (0.65)	3.8 (0.56)	3.9 (0.64)	3.9 (0.63)
Visit 8						
n/N	126/141	68/72	128/144	64/72	254/285	132/144
Mean (SD)	3.9 (0.71)	3.8 (0.76)	3.9 (0.73)	3.8 (0.66)	3.9 (0.72)	3.8 (0.71)
Visit 9						
n/N	123/141	63/72	126/144	63/72	249/285	126/144
Mean (SD)	3.9 (0.65)	3.9 (0.90)	4.0 (0.68)	3.8 (0.69)	3.9 (0.67)	3.8 (0.81)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.14.1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Visit 10						
n/N	116/141	64/72	125/144	59/72	241/285	123/144
Mean (SD)	3.8 (0.67)	3.8 (0.68)	4.0 (0.77)	3.8 (0.59)	3.9 (0.73)	3.8 (0.64)
Visit 11						
n/N	111/141	59/72	112/144	57/72	223/285	116/144
Mean (SD)	3.9 (0.75)	4.0 (0.74)	4.0 (0.79)	3.7 (0.56)	4.0 (0.77)	3.9 (0.66)
Visit 12						
n/N	113/141	62/72	119/144	59/72	232/285	121/144
Mean (SD)	3.9 (0.70)	4.0 (0.72)	4.0 (0.81)	3.8 (0.71)	3.9 (0.76)	3.9 (0.72)
Visit 13/ET						
n/N	131/141	68/72	132/144	62/72	263/285	130/144
Mean (SD)	3.9 (0.70)	3.9 (0.66)	4.0 (0.74)	3.7 (0.71)	4.0 (0.72)	3.8 (0.69)
EAP						
n/N	131/141	69/72	136/144	65/72	267/285	134/144
Mean (SD)	3.9 (0.62)	3.9 (0.58)	4.0 (0.68)	3.8 (0.53)	3.9 (0.66)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.14.1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.0 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.09, 0.29]	[-0.05, 0.22]	[0.14, 0.35]	[-0.12, 0.19]	[0.14, 0.29]	[-0.05, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.21		0.16	
95% CI	[-0.06, 0.27]		[0.02, 0.40]		[0.04, 0.28]	
p-value	0.2188		0.0282		0.0122	
heterogeneity p-value					0.4175	
Hedges' g	0.23		0.29		0.26	
95% CI	[-0.06, 0.52]		[-0.01, 0.59]		[0.05, 0.47]	
heterogeneity p-value					0.7711	
I^2					0.0%	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.05)	0.2 (0.04)	0.1 (0.06)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.09, 0.24]	[0.02, 0.22]	[0.15, 0.32]	[-0.05, 0.19]	[0.15, 0.26]	[0.02, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.17		0.10	
95% CI	[-0.08, 0.17]		[0.02, 0.31]		[0.01, 0.20]	
p-value	0.4892		0.0266		0.0321	
heterogeneity p-value					0.2164	
Hedges' g	0.16		0.28		0.22	
95% CI	[-0.13, 0.45]		[-0.02, 0.57]		[0.01, 0.43]	
heterogeneity p-value					0.5767	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.19.1.1
Number (n, %) of Subjects with Hyperphosphatemia (two consecutive visits with serum P >5.5 mg/dL) Deemed to Be Study Drug Related
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
EAP						
n/N (%)	0/141 (0.0)	0/72 (0.0)	4/144 (2.8)	1/72 (1.4)	4/285 (1.4)	1/144 (0.7)
RR [95%-CI]; p-value	NA		2.00 [0.23, 17.57], 0.5318		2.02 [0.23, 17.92], 0.5274	
OR [95%-CI]; p-value	NA		2.03 [0.22, 18.49], 0.5222		2.04 [0.23, 18.38], 0.5182	
RD [95%-CI]; p-value	NA		0.01 [-0.02, 0.05], 0.4749		0.01 [-0.01, 0.03], 0.4703	
heterogeneity (RR)						
p-value					0.5507	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5315	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; P: Phosphorus; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_19_1_1_m_hyperp.sas using SAS 9.4

Table 12.5.1.1.1
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	97/141	41/72	84/144	47/72	181/285	88/144
Mean (SD)	47.2 (50.89)	44.8 (35.09)	34.9 (24.71)	35.7 (29.87)	41.5 (41.24)	39.9 (32.53)
Visit 8						
n/N	81/141	30/72	70/144	35/72	151/285	65/144
Mean (SD)	47.3 (59.55)	50.8 (40.94)	34.2 (31.32)	34.0 (23.84)	41.2 (48.84)	41.8 (33.65)
Visit 13/ET						
n/N	77/141	26/72	75/144	28/72	152/285	54/144
Mean (SD)	51.3 (49.48)	54.1 (58.67)	60.5 (68.33)	62.1 (55.99)	55.8 (59.51)	58.3 (56.90)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.0 (6.43)	6.7 (10.91)	31.0 (9.81)	22.8 (14.75)	18.7 (5.67)	14.6 (9.02)
95% CI	[-5.76, 19.79]	[-14.97, 28.38]	[11.50, 50.60]	[-6.58, 52.19]	[7.49, 29.89]	[-3.19, 32.42]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.31		8.24		4.07	
95% CI	[-24.87, 25.49]		[-27.13, 43.62]		[-16.99, 25.13]	
p-value	0.9804		0.6439		0.7031	
heterogeneity p-value					0.7370	
Hedges' g	0.09		0.17		0.11	
95% CI	[-0.37, 0.55]		[-0.30, 0.65]		[-0.22, 0.44]	
heterogeneity p-value					0.8015	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline

Table 12.4.12.1.2
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m ^{2})
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	141/141	72/72	143/144	72/72	284/285	144/144
Mean (SD)	30.3 (11.07)	32.3 (11.02)	31.0 (9.93)	31.8 (9.61)	30.6 (10.50)	32.0 (10.31)
Visit 8						
n/N	125/141	68/72	128/144	64/72	253/285	132/144
Mean (SD)	30.1 (11.17)	31.5 (11.10)	30.7 (10.30)	31.8 (9.63)	30.4 (10.72)	31.6 (10.38)
Visit 13/ET						
n/N	131/141	68/72	132/144	62/72	263/285	130/144
Mean (SD)	29.8 (11.84)	32.0 (11.34)	29.4 (11.51)	30.4 (10.57)	29.6 (11.66)	31.2 (10.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.61)	-0.4 (0.85)	-1.4 (0.52)	-1.2 (0.77)	-0.9 (0.41)	-0.8 (0.58)
95% CI	[-1.67, 0.76]	[-2.06, 1.31]	[-2.41, -0.34]	[-2.70, 0.31]	[-1.70, -0.11]	[-1.95, 0.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.08		-0.18		-0.09	
95% CI	[-2.16, 2.00]		[-2.01, 1.65]		[-1.48, 1.30]	
p-value	0.9404		0.8444		0.8977	
heterogeneity p-value					0.8404	
Hedges' g	0.04		-0.03		0.01	
95% CI	[-0.25, 0.33]		[-0.33, 0.27]		[-0.20, 0.22]	
heterogeneity p-value					0.7543	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.15.1.1
Summary of laboratory concentration Change from Baseline for Albumin/Creatinine (g/g Creatinine)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Baseline						
n/N	116/141	62/72	110/144	55/72	226/285	117/144
Mean (SD)	0.6 (0.76)	0.7 (0.90)	0.8 (1.03)	0.9 (1.21)	0.7 (0.91)	0.8 (1.06)
Visit 8						
n/N	103/141	55/72	95/144	46/72	198/285	101/144
Mean (SD)	0.6 (0.62)	0.7 (0.88)	0.7 (0.98)	0.7 (0.93)	0.7 (0.81)	0.7 (0.90)
Visit 13/ET						
n/N	105/141	60/72	97/144	43/72	202/285	103/144
Mean (SD)	0.7 (1.10)	0.6 (0.87)	0.9 (1.32)	0.9 (1.63)	0.8 (1.21)	0.7 (1.25)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.0 (0.10)	0.1 (0.10)	0.2 (0.15)	0.1 (0.06)	0.1 (0.09)
95% CI	[-0.07, 0.21]	[-0.17, 0.21]	[-0.06, 0.33]	[-0.13, 0.47]	[-0.02, 0.22]	[-0.07, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		-0.03		0.01	
95% CI	[-0.19, 0.28]		[-0.39, 0.33]		[-0.20, 0.21]	
p-value	0.6905		0.8560		0.9441	
heterogeneity p-value					0.7172	
Hedges' g	0.06		-0.03		0.02	
95% CI	[-0.26, 0.38]		[-0.40, 0.33]		[-0.22, 0.26]	
heterogeneity p-value					0.7047	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline

Nachberechnungsdokument

Sicherheitsendpunkte
Sicherheits-relevante sHPT-assoziierte Parameter (PP-Population)

Folgende Daten werden für die PP-Population dargestellt:

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperkalzämie
- Anteil Patienten mit einer Hyperkalzurie

- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperphosphatämie

- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum

- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

Table 12.4.12.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	9.2 (0.27)	9.2 (0.27)	9.2 (0.32)	9.3 (0.27)	9.2 (0.30)	9.2 (0.27)
Visit 8						
n/N	114/115	62/62	117/119	58/60	231/234	120/122
Mean (SD)	9.3 (0.48)	9.3 (0.45)	9.4 (0.39)	9.3 (0.51)	9.4 (0.44)	9.3 (0.48)
Visit 13/ET						
n/N	115/115	61/62	117/119	57/60	232/234	118/122
Mean (SD)	9.5 (0.40)	9.3 (0.33)	9.5 (0.38)	9.4 (0.55)	9.5 (0.39)	9.3 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.03)	0.1 (0.04)	0.3 (0.03)	0.1 (0.05)	0.3 (0.02)	0.1 (0.03)
95% CI	[0.20, 0.33]	[0.03, 0.20]	[0.24, 0.37]	[0.01, 0.20]	[0.24, 0.33]	[0.05, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.15		0.20		0.17	
95% CI	[0.05, 0.26]		[0.08, 0.31]		[0.10, 0.25]	
p-value	0.0050		0.0009		<0.0001	
heterogeneity p-value					0.6253	
Hedges' g	0.48		0.54		0.52	
95% CI	[0.17, 0.80]		[0.22, 0.86]		[0.29, 0.74]	
heterogeneity p-value					0.7973	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.19.1.2.s10
Number (n, %) of Subjects with Hypercalcemia (two consecutive visits with serum Ca >10.3 mg/dL) Deemed to Be Study Drug Related
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
EAP						
n/N (%)	2/115 (1.7)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	2/234 (0.9)	0/122 (0.0)
RR [95%-CI]; p-value	2.17 [0.10, 47.47], 0.6216		NA		2.09 [0.10, 46.08], 0.6394	
OR [95%-CI]; p-value	2.19 [0.10, 49.43], 0.6121		NA		2.10 [0.09, 47.01], 0.6313	
RD [95%-CI]; p-value	0.01 [-0.02, 0.04], 0.5716		NA		0.00 [-0.01, 0.02], 0.5919	
heterogeneity (RR)						
p-value					0.5661	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5518	

Abbreviations: Ca: Calcium; CI: Confidence Interval; ER: Extended Release; PP:Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_19_1_2_m_hyperca_pp.sas using SAS 9.4

Table 12.4.15.1.3.s10
Number (n, %) of Subjects with Hypercalciuria (>200 mg calcium/g creatinine)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Visit 13/ET						
n/N (%)	1/115 (0.9)	1/62 (1.6)	3/119 (2.5)	1/60 (1.7)	4/234 (1.7)	2/122 (1.6)
RR [95%-CI]; p-value	0.54 [0.03, 8.47], 0.6602		1.51 [0.16, 14.23], 0.7175		1.04 [0.19, 5.61], 0.9611	
OR [95%-CI]; p-value	0.54 [0.03, 8.70], 0.6553		1.53 [0.16, 14.99], 0.7151		1.04 [0.19, 5.78], 0.9611	
RD [95%-CI]; p-value	-0.01 [-0.04, 0.03], 0.6828		0.01 [-0.03, 0.05], 0.6965		0.00 [-0.03, 0.03], 0.9609	
heterogeneity (RR)						
p-value					0.5691	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP:Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_15_1_3_m_hyperuca_pp.sas using SAS 9.4

Table 12.4.14.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	3.7 (0.54)	3.8 (0.59)	3.8 (0.57)	3.6 (0.44)	3.8 (0.56)	3.7 (0.53)
Visit 5						
n/N	115/115	60/62	119/119	60/60	234/234	120/122
Mean (SD)	3.8 (0.69)	3.8 (0.69)	3.9 (0.62)	3.8 (0.68)	3.8 (0.65)	3.8 (0.68)
Visit 6						
n/N	114/115	62/62	119/119	60/60	233/234	122/122
Mean (SD)	3.8 (0.59)	3.9 (0.69)	4.0 (0.68)	3.8 (0.78)	3.9 (0.64)	3.9 (0.73)
Visit 7						
n/N	106/115	58/62	111/119	52/60	217/234	110/122
Mean (SD)	3.9 (0.64)	3.9 (0.68)	3.9 (0.63)	3.8 (0.56)	3.9 (0.64)	3.8 (0.63)
Visit 8						
n/N	114/115	62/62	117/119	59/60	231/234	121/122
Mean (SD)	3.8 (0.69)	3.8 (0.77)	3.9 (0.73)	3.8 (0.66)	3.9 (0.71)	3.8 (0.72)
Visit 9						
n/N	114/115	60/62	118/119	60/60	232/234	120/122
Mean (SD)	3.9 (0.65)	3.9 (0.90)	4.0 (0.68)	3.7 (0.70)	3.9 (0.67)	3.8 (0.81)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.14.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Visit 10						
n/N	113/115	62/62	118/119	58/60	231/234	120/122
Mean (SD)	3.8 (0.68)	3.8 (0.68)	4.0 (0.77)	3.8 (0.59)	3.9 (0.73)	3.8 (0.64)
Visit 11						
n/N	109/115	57/62	107/119	56/60	216/234	113/122
Mean (SD)	3.9 (0.76)	3.9 (0.71)	4.0 (0.80)	3.7 (0.56)	4.0 (0.78)	3.8 (0.64)
Visit 12						
n/N	111/115	60/62	114/119	59/60	225/234	119/122
Mean (SD)	3.9 (0.70)	4.0 (0.72)	4.0 (0.82)	3.8 (0.71)	4.0 (0.76)	3.9 (0.72)
Visit 13/ET						
n/N	115/115	61/62	117/119	57/60	232/234	118/122
Mean (SD)	3.9 (0.71)	3.9 (0.65)	4.0 (0.73)	3.7 (0.72)	4.0 (0.72)	3.8 (0.69)
EAP						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	3.9 (0.62)	3.9 (0.57)	4.0 (0.67)	3.7 (0.53)	3.9 (0.65)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/T12_4_14_1_m_phos_pp.sas using SAS 9.4

Table 12.4.14.1.s10
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.06)	0.0 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.06, 0.27]	[-0.06, 0.23]	[0.14, 0.37]	[-0.11, 0.21]	[0.14, 0.29]	[-0.04, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.21		0.15	
95% CI	[-0.09, 0.26]		[0.01, 0.40]		[0.02, 0.28]	
p-value	0.3453		0.0375		0.0257	
heterogeneity p-value					0.3552	
Hedges' g	0.18		0.27		0.23	
95% CI	[-0.13, 0.49]		[-0.04, 0.59]		[0.01, 0.45]	
heterogeneity p-value					0.6697	
I^2					0.0%	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.04)	0.1 (0.05)	0.3 (0.04)	0.1 (0.06)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.07, 0.22]	[0.03, 0.24]	[0.17, 0.34]	[-0.03, 0.21]	[0.14, 0.25]	[0.03, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.16		0.09	
95% CI	[-0.11, 0.14]		[0.01, 0.31]		[-0.01, 0.18]	
p-value	0.8354		0.0338		0.0814	
heterogeneity p-value					0.1388	
Hedges' g	0.07		0.26		0.17	
95% CI	[-0.24, 0.38]		[-0.05, 0.57]		[-0.05, 0.39]	
heterogeneity p-value					0.3862	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.19.1.1.s10
Number (n, %) of Subjects with Hyperphosphatemia (two consecutive visits with serum P >5.5 mg/dL) Deemed to Be Study Drug Related
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
EAP						
n/N (%)	0/115 (0.0)	0/62 (0.0)	4/119 (3.4)	1/60 (1.7)	4/234 (1.7)	1/122 (0.8)
RR [95%-CI]; p-value	NA		2.02 [0.23, 17.65], 0.5262		2.09 [0.24, 18.46], 0.5088	
OR [95%-CI]; p-value	NA		2.05 [0.22, 18.78], 0.5160		2.10 [0.23, 19.04], 0.4984	
RD [95%-CI]; p-value	NA		0.02 [-0.03, 0.06], 0.4683		0.01 [-0.01, 0.03], 0.4495	
heterogeneity (RR)						
p-value					0.5640	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5457	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP:Per-Protocol; P: Phosphorus; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_19_1_1_m_hyperp_pp.sas using SAS 9.4

Table 12.5.1.1.1.s10
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	80/115	35/62	69/119	39/60	149/234	74/122
Mean (SD)	47.3 (53.61)	42.9 (35.42)	34.4 (25.26)	34.1 (25.80)	41.4 (43.23)	38.3 (30.83)
Visit 8						
n/N	72/115	26/62	62/119	33/60	134/234	59/122
Mean (SD)	41.8 (32.25)	46.8 (38.67)	33.6 (30.69)	33.8 (24.45)	38.0 (31.69)	39.5 (31.89)
Visit 13/ET						
n/N	69/115	22/62	67/119	25/60	136/234	47/122
Mean (SD)	48.5 (47.27)	42.3 (31.42)	61.4 (70.77)	63.3 (58.33)	54.9 (60.14)	53.4 (48.35)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	4.2 (5.81)	-5.4 (10.15)	34.5 (10.83)	27.8 (16.38)	19.0 (5.86)	11.0 (9.48)
95% CI	[-7.38, 15.75]	[-25.59, 14.82]	[12.91, 56.17]	[-4.86, 60.55]	[7.42, 30.56]	[-7.77, 29.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	9.57		6.69		8.03	
95% CI	[-13.71, 32.85]		[-32.52, 45.91]		[-14.00, 30.05]	
p-value	0.4158		0.7344		0.4726	
heterogeneity p-value					0.8829	
Hedges' g	0.18		0.10		0.11	
95% CI	[-0.32, 0.68]		[-0.41, 0.61]		[-0.25, 0.46]	
heterogeneity p-value					0.8243	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline

Table 12.4.12.1.2.s10
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m ^{2})
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	115/115	62/62	119/119	60/60	234/234	122/122
Mean (SD)	30.3 (10.99)	33.3 (11.05)	30.8 (9.46)	32.5 (9.25)	30.6 (10.22)	32.9 (10.17)
Visit 8						
n/N	113/115	62/62	117/119	59/60	230/234	121/122
Mean (SD)	30.7 (11.10)	32.4 (11.01)	30.7 (10.08)	31.4 (9.92)	30.7 (10.57)	31.9 (10.46)
Visit 13/ET						
n/N	115/115	61/62	117/119	57/60	232/234	118/122
Mean (SD)	30.0 (11.80)	32.9 (11.43)	29.1 (11.24)	30.9 (10.64)	29.6 (11.50)	31.9 (11.05)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.67)	-0.4 (0.93)	-1.4 (0.56)	-1.2 (0.81)	-0.9 (0.44)	-0.8 (0.62)
95% CI	[-1.82, 0.84]	[-2.19, 1.47]	[-2.48, -0.26]	[-2.83, 0.35]	[-1.78, -0.05]	[-2.04, 0.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.13		-0.13		-0.10	
95% CI	[-2.40, 2.15]		[-2.07, 1.82]		[-1.60, 1.40]	
p-value	0.9130		0.8962		0.9000	
heterogeneity p-value					0.8108	
Hedges' g	0.05		-0.02		0.02	
95% CI	[-0.26, 0.36]		[-0.34, 0.30]		[-0.20, 0.24]	
heterogeneity p-value					0.7427	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline

Table 12.4.15.1.1.s10
Summary of laboratory concentration Change from Baseline for Albumin/Creatinine (g/g Creatinine)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Baseline						
n/N	93/115	53/62	89/119	46/60	182/234	99/122
Mean (SD)	0.6 (0.79)	0.7 (0.96)	0.7 (0.96)	0.8 (1.22)	0.7 (0.87)	0.7 (1.08)
Visit 8						
n/N	94/115	49/62	88/119	41/60	182/234	90/122
Mean (SD)	0.6 (0.62)	0.7 (0.85)	0.7 (1.00)	0.7 (0.87)	0.7 (0.83)	0.7 (0.85)
Visit 13/ET						
n/N	93/115	54/62	86/119	39/60	179/234	93/122
Mean (SD)	0.7 (1.03)	0.7 (0.88)	0.8 (1.05)	0.6 (0.74)	0.8 (1.04)	0.6 (0.82)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.0 (0.09)	0.1 (0.08)	-0.1 (0.11)	0.1 (0.05)	-0.0 (0.07)
95% CI	[-0.07, 0.20]	[-0.16, 0.19]	[-0.04, 0.26]	[-0.29, 0.17]	[-0.01, 0.19]	[-0.16, 0.12]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.06		0.17		0.11	
95% CI	[-0.17, 0.28]		[-0.11, 0.44]		[-0.06, 0.28]	
p-value	0.6123		0.2292		0.2162	
heterogeneity p-value					0.5519	
Hedges' g	0.09		0.20		0.14	
95% CI	[-0.25, 0.42]		[-0.19, 0.58]		[-0.11, 0.39]	
heterogeneity p-value					0.6700	
I^2					0.0%	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The heterogeneity p-value for the difference of LS-mean is from study-by-treatment interaction effect. The heterogeneity p-value for Hedges' g and I^2 are calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline

Nachberechnungsdokument
Sicherheitsendpunkte
Unerwünschte Ereignisse
(ITT-Population)

Folgende Daten werden für die ITT-Population dargestellt:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (SMQs)
  - UE ohne erkrankungsbezogene Ereignisse
  - UE nach SOC, die zum Abbruch führten
  - UE nach PT, die zum Abbruch führten

Table 12.4.3.1
Overall Summary of Treatment-Emmergent Adverse Events
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE						
n/N (%)	101/141 (71.6)	56/72 (77.8)	91/144 (63.2)	44/72 (61.1)	192/285 (67.4)	100/144 (69.4)
RR [95%-CI]; p-value	0.92 [0.78, 1.08], 0.3173		1.03 [0.83, 1.29], 0.7677		0.97 [0.85, 1.11], 0.6598	
OR [95%-CI]; p-value	0.72 [0.37, 1.40], 0.3351		1.09 [0.61, 1.96], 0.7656		0.91 [0.59, 1.40], 0.6632	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3214		0.02 [-0.12, 0.16], 0.7664		-0.02 [-0.11, 0.07], 0.6613	
heterogeneity (RR)						
p-value					0.4087	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3571	
Number of patients with drug-related AE						
n/N (%)	17/141 (12.1)	11/72 (15.3)	19/144 (13.2)	2/72 (2.8)	36/285 (12.6)	13/144 (9.0)
RR [95%-CI]; p-value	0.79 [0.39, 1.59], 0.5093		4.75 [1.14, 19.83], 0.0326		1.40 [0.77, 2.55], 0.2739	
OR [95%-CI]; p-value	0.76 [0.34, 1.72], 0.5105		5.32 [1.20, 23.51], 0.0149		1.46 [0.75, 2.84], 0.2678	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.5235		0.10 [0.04, 0.17], 0.0023		0.04 [-0.02, 0.10], 0.2442	
heterogeneity (RR)						
p-value					0.0272	
I^2					79.5%	
heterogeneity (OR)						
p-value					0.0161	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1
Overall Summary of Treatment-Emmergent Adverse Events
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with severe AE						
n/N (%)	18/141 (12.8)	6/72 (8.3)	10/144 (6.9)	7/72 (9.7)	28/285 (9.8)	13/144 (9.0)
RR [95%-CI]; p-value	1.53 [0.64, 3.69], 0.3417		0.71 [0.28, 1.80], 0.4752		1.09 [0.58, 2.04], 0.7913	
OR [95%-CI]; p-value	1.61 [0.61, 4.25], 0.3331		0.69 [0.25, 1.90], 0.4748		1.10 [0.55, 2.19], 0.7910	
RD [95%-CI]; p-value	0.04 [-0.04, 0.13], 0.3028		-0.03 [-0.11, 0.05], 0.4964		0.01 [-0.05, 0.07], 0.7884	
heterogeneity (RR)						
p-value					0.2409	
I^2					27.3%	
heterogeneity (OR)						
p-value					0.2349	
Number of Patients with SAE						
n/N (%)	30/141 (21.3)	12/72 (16.7)	22/144 (15.3)	11/72 (15.3)	52/285 (18.2)	23/144 (16.0)
RR [95%-CI]; p-value	1.28 [0.70, 2.34], 0.4299		1.00 [0.51, 1.95], 1.0000		1.14 [0.73, 1.79], 0.5605	
OR [95%-CI]; p-value	1.35 [0.65, 2.83], 0.4238		1.00 [0.46, 2.20], 1.0000		1.17 [0.69, 2.01], 0.5583	
RD [95%-CI]; p-value	0.05 [-0.06, 0.16], 0.4090		0.00 [-0.10, 0.10], 1.0000		0.02 [-0.05, 0.10], 0.5512	
heterogeneity (RR)						
p-value					0.5952	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5843	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1
Overall Summary of Treatment-Emmergent Adverse Events
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE leading to treatment discontiuation						
n/N (%)	16/141 (11.3)	5/72 (6.9)	15/144 (10.4)	4/72 (5.6)	31/285 (10.9)	9/144 (6.3)
RR [95%-CI]; p-value	1.63 [0.62, 4.28], 0.3177		1.88 [0.65, 5.44], 0.2478		1.74 [0.85, 3.56], 0.1286	
OR [95%-CI]; p-value	1.72 [0.60, 4.89], 0.3079		1.98 [0.63, 6.19], 0.2344		1.83 [0.85, 3.96], 0.1196	
RD [95%-CI]; p-value	0.04 [-0.03, 0.12], 0.2726		0.05 [-0.02, 0.12], 0.1902		0.05 [-0.01, 0.10], 0.0905	
heterogeneity (RR)						
p-value					0.8512	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8574	
Number of Patients with AE leading to study discontinuation						
n/N (%)	8/141 (5.7)	2/72 (2.8)	7/144 (4.9)	3/72 (4.2)	15/285 (5.3)	5/144 (3.5)
RR [95%-CI]; p-value	2.04 [0.45, 9.37], 0.3581		1.17 [0.31, 4.38], 0.8193		1.52 [0.56, 4.09], 0.4112	
OR [95%-CI]; p-value	2.11 [0.44, 10.18], 0.3446		1.18 [0.29, 4.69], 0.8189		1.54 [0.55, 4.34], 0.4060	
RD [95%-CI]; p-value	0.03 [-0.02, 0.08], 0.2918		0.01 [-0.05, 0.06], 0.8145		0.02 [-0.02, 0.06], 0.3751	
heterogeneity (RR)						
p-value					0.5864	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5838	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1
Overall Summary of Treatment-Emmergent Adverse Events
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE leading to death						
n/N (%)	3/141 (2.1)	1/72 (1.4)	3/144 (2.1)	1/72 (1.4)	6/285 (2.1)	2/144 (1.4)
RR [95%-CI]; p-value	1.53 [0.16, 14.47], 0.7097		1.50 [0.16, 14.17], 0.7234		1.52 [0.31, 7.42], 0.6076	
OR [95%-CI]; p-value	1.54 [0.16, 15.11], 0.7071		1.51 [0.15, 14.78], 0.7212		1.53 [0.30, 7.66], 0.6045	
RD [95%-CI]; p-value	0.01 [-0.03, 0.04], 0.6878		0.01 [-0.03, 0.04], 0.7031		0.01 [-0.02, 0.03], 0.5798	
heterogeneity (RR)						
p-value					0.9896	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9896	
Number of Patients with AE by severity						
Mild						
n/N (%)	82/141 (58.2)	50/72 (69.4)	70/144 (48.6)	35/72 (48.6)	152/285 (53.3)	85/144 (59.0)
RR* [95%-CI]; p-value	0.84 [0.68, 1.03], 0.0939		1.00 [0.75, 1.34], 1.0000		0.90 [0.76, 1.08], 0.2534	
OR* [95%-CI]; p-value	0.61 [0.33, 1.12], 0.1084		1.00 [0.57, 1.76], 1.0000		0.79 [0.53, 1.19], 0.2627	
RD* [95%-CI]; p-value	-0.11 [-0.25, 0.02], 0.0987		0.00 [-0.14, 0.14], 1.0000		-0.06 [-0.16, 0.04], 0.2597	
heterogeneity (RR)						
p-value					0.3305	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.2433	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1
Overall Summary of Treatment-Emmergent Adverse Events
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
n/N (%)	50/141 (35.5)	29/72 (40.3)	49/144 (34.0)	18/72 (25.0)	99/285 (34.7)	47/144 (32.6)
RR* [95%-CI]; p-value	0.88 [0.62, 1.26], 0.4865		1.36 [0.86, 2.16], 0.1892		1.06 [0.80, 1.41], 0.6667	
OR* [95%-CI]; p-value	0.81 [0.45, 1.46], 0.4912		1.55 [0.82, 2.92], 0.1763		1.10 [0.72, 1.68], 0.6650	
RD* [95%-CI]; p-value	-0.05 [-0.19, 0.09], 0.4942		0.09 [-0.04, 0.22], 0.1618		0.02 [-0.07, 0.12], 0.6633	
heterogeneity (RR)						
p-value					0.1434	
I^2					53.3%	
heterogeneity (OR)						
p-value					0.1442	
Severe						
n/N (%)	18/141 (12.8)	6/72 (8.3)	10/144 (6.9)	7/72 (9.7)	28/285 (9.8)	13/144 (9.0)
RR* [95%-CI]; p-value	1.53 [0.64, 3.69], 0.3417		0.71 [0.28, 1.80], 0.4752		1.09 [0.58, 2.04], 0.7913	
OR* [95%-CI]; p-value	1.61 [0.61, 4.25], 0.3331		0.69 [0.25, 1.90], 0.4748		1.10 [0.55, 2.19], 0.7910	
RD* [95%-CI]; p-value	0.04 [-0.04, 0.13], 0.3028		-0.03 [-0.11, 0.05], 0.4964		0.01 [-0.05, 0.07], 0.7884	
heterogeneity (RR)						
p-value					0.2409	
I^2					27.3%	
heterogeneity (OR)						
p-value					0.2349	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
n/N (%)	11/141 (7.8)	9/72 (12.5)	11/144 (7.6)	4/72 (5.6)	22/285 (7.7)	13/144 (9.0)
RR [95%-CI]; p-value	0.62 [0.27, 1.44], 0.2679		1.38 [0.45, 4.17], 0.5735		0.86 [0.44, 1.65], 0.6398	
OR [95%-CI]; p-value	0.59 [0.23, 1.50], 0.2661		1.41 [0.43, 4.58], 0.5702		0.84 [0.41, 1.73], 0.6401	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.04], 0.2969		0.02 [-0.05, 0.09], 0.5507		-0.01 [-0.07, 0.04], 0.6478	
heterogeneity (RR)						
p-value					0.2645	
I^2					19.7%	
heterogeneity (OR)						
p-value					0.2559	
Gastrointestinal disorders						
n/N (%)	28/141 (19.9)	20/72 (27.8)	26/144 (18.1)	7/72 (9.7)	54/285 (18.9)	27/144 (18.8)
RR [95%-CI]; p-value	0.71 [0.43, 1.18], 0.1871		1.86 [0.85, 4.07], 0.1223		1.01 [0.67, 1.53], 0.9607	
OR [95%-CI]; p-value	0.64 [0.33, 1.25], 0.1907		2.05 [0.84, 4.97], 0.1085		1.01 [0.61, 1.69], 0.9607	
RD [95%-CI]; p-value	-0.08 [-0.20, 0.04], 0.2056		0.08 [-0.01, 0.18], 0.0787		0.00 [-0.08, 0.08], 0.9606	
heterogeneity (RR)						
p-value					0.0443	
I^2					75.3%	
heterogeneity (OR)						
p-value					0.0382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
n/N (%)	19/141 (13.5)	15/72 (20.8)	17/144 (11.8)	11/72 (15.3)	36/285 (12.6)	26/144 (18.1)
RR [95%-CI]; p-value	0.65 [0.35, 1.20], 0.1647		0.77 [0.38, 1.56], 0.4727		0.70 [0.44, 1.11], 0.1304	
OR [95%-CI]; p-value	0.59 [0.28, 1.25], 0.1654		0.74 [0.33, 1.68], 0.4739		0.66 [0.38, 1.14], 0.1314	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.1876		-0.03 [-0.13, 0.06], 0.4892		-0.05 [-0.13, 0.02], 0.1493	
heterogeneity (RR)						
p-value					0.7090	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6882	
Infections and infestations						
n/N (%)	38/141 (27.0)	20/72 (27.8)	33/144 (22.9)	16/72 (22.2)	71/285 (24.9)	36/144 (25.0)
RR [95%-CI]; p-value	0.97 [0.61, 1.54], 0.8977		1.03 [0.61, 1.74], 0.9087		1.00 [0.70, 1.41], 0.9842	
OR [95%-CI]; p-value	0.96 [0.51, 1.81], 0.8979		1.04 [0.53, 2.05], 0.9085		1.00 [0.63, 1.58], 0.9842	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8982		0.01 [-0.11, 0.12], 0.9082		-0.00 [-0.09, 0.09], 0.9842	
heterogeneity (RR)						
p-value					0.8642	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8638	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
n/N (%)	17/141 (12.1)	5/72 (6.9)	11/144 (7.6)	3/72 (4.2)	28/285 (9.8)	8/144 (5.6)
RR [95%-CI]; p-value	1.74 [0.67, 4.52], 0.2580		1.83 [0.53, 6.37], 0.3399		1.77 [0.83, 3.78], 0.1414	
OR [95%-CI]; p-value	1.84 [0.65, 5.20], 0.2462		1.90 [0.51, 7.05], 0.3285		1.85 [0.82, 4.17], 0.1321	
RD [95%-CI]; p-value	0.05 [-0.03, 0.13], 0.2081		0.03 [-0.03, 0.10], 0.2827		0.04 [-0.01, 0.09], 0.1004	
heterogeneity (RR)						
p-value					0.9458	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9674	
Investigations						
n/N (%)	17/141 (12.1)	10/72 (13.9)	14/144 (9.7)	7/72 (9.7)	31/285 (10.9)	17/144 (11.8)
RR [95%-CI]; p-value	0.87 [0.42, 1.80], 0.7032		1.00 [0.42, 2.37], 1.0000		0.92 [0.53, 1.61], 0.7730	
OR [95%-CI]; p-value	0.85 [0.37, 1.97], 0.7038		1.00 [0.38, 2.60], 1.0000		0.91 [0.49, 1.71], 0.7733	
RD [95%-CI]; p-value	-0.02 [-0.11, 0.08], 0.7092		0.00 [-0.08, 0.08], 1.0000		-0.01 [-0.07, 0.05], 0.7759	
heterogeneity (RR)						
p-value					0.8059	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8020	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
n/N (%)	28/141 (19.9)	21/72 (29.2)	25/144 (17.4)	13/72 (18.1)	53/285 (18.6)	34/144 (23.6)
RR [95%-CI]; p-value	0.68 [0.42, 1.11], 0.1237		0.96 [0.52, 1.77], 0.8993		0.79 [0.54, 1.15], 0.2196	
OR [95%-CI]; p-value	0.60 [0.31, 1.16], 0.1268		0.95 [0.46, 2.00], 0.8994		0.74 [0.45, 1.20], 0.2225	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1410		-0.01 [-0.12, 0.10], 0.9000		-0.05 [-0.13, 0.03], 0.2351	
heterogeneity (RR)						
p-value					0.3858	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3606	
Musculoskeletal and connective tissue disorders						
n/N (%)	24/141 (17.0)	23/72 (31.9)	22/144 (15.3)	14/72 (19.4)	46/285 (16.1)	37/144 (25.7)
RR [95%-CI]; p-value	0.53 [0.32, 0.88], 0.0129		0.79 [0.43, 1.44], 0.4365		0.63 [0.43, 0.92], 0.0175	
OR [95%-CI]; p-value	0.44 [0.23, 0.85], 0.0130		0.75 [0.36, 1.56], 0.4386		0.56 [0.34, 0.91], 0.0180	
RD [95%-CI]; p-value	-0.15 [-0.27, -0.02], 0.0186		-0.04 [-0.15, 0.07], 0.4524		-0.10 [-0.18, -0.01], 0.0244	
heterogeneity (RR)						
p-value					0.3319	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.2888	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/T12_4_4_1_1_m_soc_ae10pct.sas using SAS 9.4

Table 12.4.4.1.1

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
n/N (%)	12/141 (8.5)	13/72 (18.1)	20/144 (13.9)	8/72 (11.1)	32/285 (11.2)	21/144 (14.6)
RR [95%-CI]; p-value	0.47 [0.23, 0.98], 0.0439		1.25 [0.58, 2.70], 0.5698		0.77 [0.46, 1.29], 0.3175	
OR [95%-CI]; p-value	0.42 [0.18, 0.98], 0.0406		1.29 [0.54, 3.09], 0.5667		0.74 [0.41, 1.34], 0.3186	
RD [95%-CI]; p-value	-0.10 [-0.20, 0.00], 0.0616		0.03 [-0.06, 0.12], 0.5539		-0.03 [-0.10, 0.03], 0.3357	
heterogeneity (RR)						
p-value					0.0718	
I^2					69.1%	
heterogeneity (OR)						
p-value					0.0685	
Respiratory, thoracic and mediastinal disorders						
n/N (%)	18/141 (12.8)	12/72 (16.7)	17/144 (11.8)	7/72 (9.7)	35/285 (12.3)	19/144 (13.2)
RR [95%-CI]; p-value	0.77 [0.39, 1.50], 0.4375		1.21 [0.53, 2.79], 0.6480		0.93 [0.55, 1.57], 0.7873	
OR [95%-CI]; p-value	0.73 [0.33, 1.62], 0.4388		1.24 [0.49, 3.15], 0.6460		0.92 [0.51, 1.68], 0.7876	
RD [95%-CI]; p-value	-0.04 [-0.14, 0.06], 0.4544		0.02 [-0.07, 0.11], 0.6364		-0.01 [-0.08, 0.06], 0.7897	
heterogeneity (RR)						
p-value					0.3992	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3941	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.1

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
n/N (%)	9/141 (6.4)	9/72 (12.5)	15/144 (10.4)	6/72 (8.3)	24/285 (8.4)	15/144 (10.4)
RR [95%-CI]; p-value	0.51 [0.21, 1.23], 0.1341		1.25 [0.51, 3.09], 0.6283		0.81 [0.44, 1.49], 0.4966	
OR [95%-CI]; p-value	0.48 [0.18, 1.26], 0.1289		1.28 [0.47, 3.45], 0.6261		0.79 [0.40, 1.56], 0.4972	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.03], 0.1652		0.02 [-0.06, 0.10], 0.6143		-0.02 [-0.08, 0.04], 0.5103	
heterogeneity (RR)						
p-value					0.1640	
I^2					48.4%	
heterogeneity (OR)						
p-value					0.1604	
Vascular disorders						
n/N (%)	15/141 (10.6)	9/72 (12.5)	11/144 (7.6)	7/72 (9.7)	26/285 (9.1)	16/144 (11.1)
RR [95%-CI]; p-value	0.85 [0.39, 1.85], 0.6838		0.79 [0.32, 1.94], 0.6012		0.82 [0.46, 1.48], 0.5122	
OR [95%-CI]; p-value	0.83 [0.35, 2.01], 0.6844		0.77 [0.28, 2.07], 0.6015		0.80 [0.42, 1.55], 0.5129	
RD [95%-CI]; p-value	-0.02 [-0.11, 0.07], 0.6910		-0.02 [-0.10, 0.06], 0.6143		-0.02 [-0.08, 0.04], 0.5247	
heterogeneity (RR)						
p-value					0.8955	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9040	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.3

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by PT

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
n/N (%)	6/141 (4.3)	12/72 (16.7)	6/144 (4.2)	0/72 (0.0)	12/285 (4.2)	12/144 (8.3)
RR [95%-CI]; p-value	0.26 [0.10, 0.65], 0.0043		6.04 [0.34, 106.68], 0.2195		0.51 [0.23, 1.10], 0.0841	
OR [95%-CI]; p-value	0.22 [0.08, 0.62], 0.0021		6.26 [0.34, 113.68], 0.1571		0.48 [0.21, 1.11], 0.0793	
RD [95%-CI]; p-value	-0.12 [-0.22, -0.03], 0.0084		0.03 [-0.00, 0.07], 0.0713		-0.04 [-0.09, 0.01], 0.1117	
heterogeneity (RR)						
p-value					0.0401	
I^2					76.3%	
heterogeneity (OR)						
p-value					0.0073	
Infections and infestations						
Urinary tract infection						
n/N (%)	7/141 (5.0)	10/72 (13.9)	7/144 (4.9)	3/72 (4.2)	14/285 (4.9)	13/144 (9.0)
RR [95%-CI]; p-value	0.36 [0.14, 0.90], 0.0290		1.17 [0.31, 4.38], 0.8193		0.54 [0.26, 1.13], 0.1013	
OR [95%-CI]; p-value	0.32 [0.12, 0.89], 0.0230		1.18 [0.29, 4.69], 0.8189		0.52 [0.24, 1.14], 0.0974	
RD [95%-CI]; p-value	-0.09 [-0.18, -0.00], 0.0458		0.01 [-0.05, 0.06], 0.8145		-0.04 [-0.09, 0.01], 0.1288	
heterogeneity (RR)						
p-value					0.1506	
I^2					51.6%	
heterogeneity (OR)						
p-value					0.1333	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.8.1.1

Summary of SAE Occurring ≥ 5% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
n/N (%)	8/141 (5.7)	3/72 (4.2)	5/144 (3.5)	3/72 (4.2)	13/285 (4.6)	6/144 (4.2)
RR [95%-CI]; p-value	1.36 [0.37, 4.98], 0.6406		0.83 [0.20, 3.39], 0.7990		1.09 [0.42, 2.82], 0.8513	
OR [95%-CI]; p-value	1.38 [0.36, 5.38], 0.6383		0.83 [0.19, 3.56], 0.7989		1.10 [0.41, 2.95], 0.8511	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.6219		-0.01 [-0.06, 0.05], 0.8045		0.00 [-0.04, 0.04], 0.8490	
heterogeneity (RR)						
p-value					0.6144	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6122	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.8.1.2
Summary of SAE Occurring ≥ 5% in One Arm by PT
ITT Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.5.1.1

Summary of Severe TEAE Occurring ≥ 5% in One Arm by SOC

ITT Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.5.1.2

Summary of Severe TEAE Occurring ≥ 5% in One Arm by PT

ITT Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.

TEAE: Treatment emergent adverse event; SOC: System Organ Class; RR: Relative Risk; OR: Odds Ratio; RD: Risk Difference.

N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
n/N (%)	11/141 (7.8)	9/72 (12.5)	11/144 (7.6)	4/72 (5.6)	22/285 (7.7)	13/144 (9.0)
RR [95%-CI]; p-value	0.62 [0.27, 1.44], 0.2679		1.38 [0.45, 4.17], 0.5735		0.86 [0.44, 1.65], 0.6398	
OR [95%-CI]; p-value	0.59 [0.23, 1.50], 0.2661		1.41 [0.43, 4.58], 0.5702		0.84 [0.41, 1.73], 0.6401	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.04], 0.2969		0.02 [-0.05, 0.09], 0.5507		-0.01 [-0.07, 0.04], 0.6478	
heterogeneity (RR)						
p-value					0.2645	
I^2					19.7%	
heterogeneity (OR)						
p-value					0.2559	
Gastrointestinal disorders						
n/N (%)	28/141 (19.9)	20/72 (27.8)	26/144 (18.1)	7/72 (9.7)	54/285 (18.9)	27/144 (18.8)
RR [95%-CI]; p-value	0.71 [0.43, 1.18], 0.1871		1.86 [0.85, 4.07], 0.1223		1.01 [0.67, 1.53], 0.9607	
OR [95%-CI]; p-value	0.64 [0.33, 1.25], 0.1907		2.05 [0.84, 4.97], 0.1085		1.01 [0.61, 1.69], 0.9607	
RD [95%-CI]; p-value	-0.08 [-0.20, 0.04], 0.2056		0.08 [-0.01, 0.18], 0.0787		0.00 [-0.08, 0.08], 0.9606	
heterogeneity (RR)						
p-value					0.0443	
I^2					75.3%	
heterogeneity (OR)						
p-value					0.0382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
n/N (%)	19/141 (13.5)	15/72 (20.8)	17/144 (11.8)	11/72 (15.3)	36/285 (12.6)	26/144 (18.1)
RR [95%-CI]; p-value	0.65 [0.35, 1.20], 0.1647		0.77 [0.38, 1.56], 0.4727		0.70 [0.44, 1.11], 0.1304	
OR [95%-CI]; p-value	0.59 [0.28, 1.25], 0.1654		0.74 [0.33, 1.68], 0.4739		0.66 [0.38, 1.14], 0.1314	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.1876		-0.03 [-0.13, 0.06], 0.4892		-0.05 [-0.13, 0.02], 0.1493	
heterogeneity (RR)						
p-value					0.7090	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6882	
Infections and infestations						
n/N (%)	38/141 (27.0)	20/72 (27.8)	33/144 (22.9)	16/72 (22.2)	71/285 (24.9)	36/144 (25.0)
RR [95%-CI]; p-value	0.97 [0.61, 1.54], 0.8977		1.03 [0.61, 1.74], 0.9087		1.00 [0.70, 1.41], 0.9842	
OR [95%-CI]; p-value	0.96 [0.51, 1.81], 0.8979		1.04 [0.53, 2.05], 0.9085		1.00 [0.63, 1.58], 0.9842	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8982		0.01 [-0.11, 0.12], 0.9082		-0.00 [-0.09, 0.09], 0.9842	
heterogeneity (RR)						
p-value					0.8642	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8638	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
n/N (%)	17/141 (12.1)	5/72 (6.9)	11/144 (7.6)	3/72 (4.2)	28/285 (9.8)	8/144 (5.6)
RR [95%-CI]; p-value	1.74 [0.67, 4.52], 0.2580		1.83 [0.53, 6.37], 0.3399		1.77 [0.83, 3.78], 0.1414	
OR [95%-CI]; p-value	1.84 [0.65, 5.20], 0.2462		1.90 [0.51, 7.05], 0.3285		1.85 [0.82, 4.17], 0.1321	
RD [95%-CI]; p-value	0.05 [-0.03, 0.13], 0.2081		0.03 [-0.03, 0.10], 0.2827		0.04 [-0.01, 0.09], 0.1004	
heterogeneity (RR)						
p-value					0.9458	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9674	
Investigations						
n/N (%)	17/141 (12.1)	10/72 (13.9)	14/144 (9.7)	7/72 (9.7)	31/285 (10.9)	17/144 (11.8)
RR [95%-CI]; p-value	0.87 [0.42, 1.80], 0.7032		1.00 [0.42, 2.37], 1.0000		0.92 [0.53, 1.61], 0.7730	
OR [95%-CI]; p-value	0.85 [0.37, 1.97], 0.7038		1.00 [0.38, 2.60], 1.0000		0.91 [0.49, 1.71], 0.7733	
RD [95%-CI]; p-value	-0.02 [-0.11, 0.08], 0.7092		0.00 [-0.08, 0.08], 1.0000		-0.01 [-0.07, 0.05], 0.7759	
heterogeneity (RR)						
p-value					0.8059	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8020	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
n/N (%)	28/141 (19.9)	21/72 (29.2)	25/144 (17.4)	13/72 (18.1)	53/285 (18.6)	34/144 (23.6)
RR [95%-CI]; p-value	0.68 [0.42, 1.11], 0.1237		0.96 [0.52, 1.77], 0.8993		0.79 [0.54, 1.15], 0.2196	
OR [95%-CI]; p-value	0.60 [0.31, 1.16], 0.1268		0.95 [0.46, 2.00], 0.8994		0.74 [0.45, 1.20], 0.2225	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1410		-0.01 [-0.12, 0.10], 0.9000		-0.05 [-0.13, 0.03], 0.2351	
heterogeneity (RR)						
p-value					0.3858	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3606	
Musculoskeletal and connective tissue disorders						
n/N (%)	24/141 (17.0)	23/72 (31.9)	22/144 (15.3)	14/72 (19.4)	46/285 (16.1)	37/144 (25.7)
RR [95%-CI]; p-value	0.53 [0.32, 0.88], 0.0129		0.79 [0.43, 1.44], 0.4365		0.63 [0.43, 0.92], 0.0175	
OR [95%-CI]; p-value	0.44 [0.23, 0.85], 0.0130		0.75 [0.36, 1.56], 0.4386		0.56 [0.34, 0.91], 0.0180	
RD [95%-CI]; p-value	-0.15 [-0.27, -0.02], 0.0186		-0.04 [-0.15, 0.07], 0.4524		-0.10 [-0.18, -0.01], 0.0244	
heterogeneity (RR)						
p-value					0.3319	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.2888	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
n/N (%)	12/141 (8.5)	13/72 (18.1)	20/144 (13.9)	8/72 (11.1)	32/285 (11.2)	21/144 (14.6)
RR [95%-CI]; p-value	0.47 [0.23, 0.98], 0.0439		1.25 [0.58, 2.70], 0.5698		0.77 [0.46, 1.29], 0.3175	
OR [95%-CI]; p-value	0.42 [0.18, 0.98], 0.0406		1.29 [0.54, 3.09], 0.5667		0.74 [0.41, 1.34], 0.3186	
RD [95%-CI]; p-value	-0.10 [-0.20, 0.00], 0.0616		0.03 [-0.06, 0.12], 0.5539		-0.03 [-0.10, 0.03], 0.3357	
heterogeneity (RR)						
p-value					0.0718	
I^2					69.1%	
heterogeneity (OR)						
p-value					0.0685	
Renal and urinary disorders						
n/N (%)	11/141 (7.8)	5/72 (6.9)	12/144 (8.3)	7/72 (9.7)	23/285 (8.1)	12/144 (8.3)
RR [95%-CI]; p-value	1.12 [0.41, 3.11], 0.8228		0.86 [0.35, 2.08], 0.7337		0.97 [0.50, 1.89], 0.9251	
OR [95%-CI]; p-value	1.13 [0.38, 3.40], 0.8224		0.84 [0.32, 2.25], 0.7341		0.97 [0.47, 2.00], 0.9251	
RD [95%-CI]; p-value	0.01 [-0.06, 0.08], 0.8193		-0.01 [-0.10, 0.07], 0.7398		-0.00 [-0.06, 0.05], 0.9254	
heterogeneity (RR)						
p-value					0.6948	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6938	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
n/N (%)	18/141 (12.8)	12/72 (16.7)	17/144 (11.8)	7/72 (9.7)	35/285 (12.3)	19/144 (13.2)
RR [95%-CI]; p-value	0.77 [0.39, 1.50], 0.4375		1.21 [0.53, 2.79], 0.6480		0.93 [0.55, 1.57], 0.7873	
OR [95%-CI]; p-value	0.73 [0.33, 1.62], 0.4388		1.24 [0.49, 3.15], 0.6460		0.92 [0.51, 1.68], 0.7876	
RD [95%-CI]; p-value	-0.04 [-0.14, 0.06], 0.4544		0.02 [-0.07, 0.11], 0.6364		-0.01 [-0.08, 0.06], 0.7897	
heterogeneity (RR)						
p-value					0.3992	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3941	
Skin and subcutaneous tissue disorders						
n/N (%)	9/141 (6.4)	9/72 (12.5)	15/144 (10.4)	6/72 (8.3)	24/285 (8.4)	15/144 (10.4)
RR [95%-CI]; p-value	0.51 [0.21, 1.23], 0.1341		1.25 [0.51, 3.09], 0.6283		0.81 [0.44, 1.49], 0.4966	
OR [95%-CI]; p-value	0.48 [0.18, 1.26], 0.1289		1.28 [0.47, 3.45], 0.6261		0.79 [0.40, 1.56], 0.4972	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.03], 0.1652		0.02 [-0.06, 0.10], 0.6143		-0.02 [-0.08, 0.04], 0.5103	
heterogeneity (RR)						
p-value					0.1640	
I^2					48.4%	
heterogeneity (OR)						
p-value					0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

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Table 12.4.4.1.2

Summary of TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
n/N (%)	15/141 (10.6)	9/72 (12.5)	11/144 (7.6)	7/72 (9.7)	26/285 (9.1)	16/144 (11.1)
RR [95%-CI]; p-value	0.85 [0.39, 1.85], 0.6838		0.79 [0.32, 1.94], 0.6012		0.82 [0.46, 1.48], 0.5122	
OR [95%-CI]; p-value	0.83 [0.35, 2.01], 0.6844		0.77 [0.28, 2.07], 0.6015		0.80 [0.42, 1.55], 0.5129	
RD [95%-CI]; p-value	-0.02 [-0.11, 0.07], 0.6910		-0.02 [-0.10, 0.06], 0.6143		-0.02 [-0.08, 0.04], 0.5247	
heterogeneity (RR)						
p-value					0.8955	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9040	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/T12_4_4_1_2_m_soc_ae1pct.sas using SAS 9.4

Table 12.4.4.1.4

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by PT

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
n/N (%)	6/141 (4.3)	12/72 (16.7)	6/144 (4.2)	0/72 (0.0)	12/285 (4.2)	12/144 (8.3)
RR [95%-CI]; p-value	0.26 [0.10, 0.65], 0.0043		6.04 [0.34, 106.68], 0.2195		0.51 [0.23, 1.10], 0.0841	
OR [95%-CI]; p-value	0.22 [0.08, 0.62], 0.0021		6.26 [0.34, 113.68], 0.1571		0.48 [0.21, 1.11], 0.0793	
RD [95%-CI]; p-value	-0.12 [-0.22, -0.03], 0.0084		0.03 [-0.00, 0.07], 0.0713		-0.04 [-0.09, 0.01], 0.1117	
heterogeneity (RR)						
p-value					0.0401	
I^2					76.3%	
heterogeneity (OR)						
p-value					0.0073	
Infections and infestations						
Urinary tract infection						
n/N (%)	7/141 (5.0)	10/72 (13.9)	7/144 (4.9)	3/72 (4.2)	14/285 (4.9)	13/144 (9.0)
RR [95%-CI]; p-value	0.36 [0.14, 0.90], 0.0290		1.17 [0.31, 4.38], 0.8193		0.54 [0.26, 1.13], 0.1013	
OR [95%-CI]; p-value	0.32 [0.12, 0.89], 0.0230		1.18 [0.29, 4.69], 0.8189		0.52 [0.24, 1.14], 0.0974	
RD [95%-CI]; p-value	-0.09 [-0.18, -0.00], 0.0458		0.01 [-0.05, 0.06], 0.8145		-0.04 [-0.09, 0.01], 0.1288	
heterogeneity (RR)						
p-value					0.1506	
I^2					51.6%	
heterogeneity (OR)						
p-value					0.1333	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.4

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by PT

ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
n/N (%)	10/141 (7.1)	5/72 (6.9)	8/144 (5.6)	6/72 (8.3)	18/285 (6.3)	11/144 (7.6)
RR [95%-CI]; p-value	1.02 [0.36, 2.88], 0.9682		0.67 [0.24, 1.85], 0.4359		0.83 [0.40, 1.70], 0.6060	
OR [95%-CI]; p-value	1.02 [0.34, 3.11], 0.9682		0.65 [0.22, 1.94], 0.4344		0.82 [0.37, 1.78], 0.6062	
RD [95%-CI]; p-value	0.00 [-0.07, 0.07], 0.9681		-0.03 [-0.10, 0.05], 0.4619		-0.01 [-0.06, 0.04], 0.6164	
heterogeneity (RR)						
p-value					0.5652	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5652	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
n/N (%)	15/141 (10.6)	2/72 (2.8)	9/144 (6.3)	7/72 (9.7)	24/285 (8.4)	9/144 (6.3)
RR [95%-CI]; p-value	3.83 [0.90, 16.29], 0.0691		0.64 [0.25, 1.66], 0.3602		1.35 [0.64, 2.82], 0.4293	
OR [95%-CI]; p-value	4.17 [0.93, 18.75], 0.0452		0.62 [0.22, 1.74], 0.3583		1.38 [0.62, 3.05], 0.4255	
RD [95%-CI]; p-value	0.08 [0.02, 0.14], 0.0152		-0.03 [-0.11, 0.04], 0.3892		0.02 [-0.03, 0.07], 0.4042	
heterogeneity (RR)						
p-value					0.0432	
I^2					75.5%	
heterogeneity (OR)						
p-value					0.0304	
Number of Patients with Any Severe SMQ of Acute Renal Failure						
n/N (%)	2/141 (1.4)	0/72 (0.0)	1/144 (0.7)	1/72 (1.4)	3/285 (1.1)	1/144 (0.7)
RR [95%-CI]; p-value	2.06 [0.09, 45.02], 0.6470		0.50 [0.03, 7.88], 0.6222		1.52 [0.16, 14.44], 0.7176	
OR [95%-CI]; p-value	2.07 [0.09, 46.55], 0.6392		0.50 [0.03, 8.05], 0.6154		1.52 [0.16, 14.76], 0.7155	
RD [95%-CI]; p-value	0.01 [-0.02, 0.03], 0.6005		-0.01 [-0.04, 0.02], 0.6527		0.00 [-0.01, 0.02], 0.6967	
heterogeneity (RR)						
p-value					0.5030	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4910	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq.sas using SAS 9.4

Table 12.4.4.1.7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
n/N (%)	13/141 (9.2)	2/72 (2.8)	8/144 (5.6)	6/72 (8.3)	21/285 (7.4)	8/144 (5.6)
RR [95%-CI]; p-value	3.32 [0.77, 14.31], 0.1076		0.67 [0.24, 1.85], 0.4359		1.33 [0.60, 2.92], 0.4831	
OR [95%-CI]; p-value	3.55 [0.78, 16.20], 0.0822		0.65 [0.22, 1.94], 0.4344		1.35 [0.58, 3.13], 0.4800	
RD [95%-CI]; p-value	0.06 [0.00, 0.13], 0.0385		-0.03 [-0.10, 0.05], 0.4619		0.02 [-0.03, 0.07], 0.4607	
heterogeneity (RR)						
p-value					0.0775	
I^2					67.9%	
heterogeneity (OR)						
p-value					0.0627	
Number of Patients with Any Serious SMQ of Acute Renal Failure						
n/N (%)	7/141 (5.0)	1/72 (1.4)	3/144 (2.1)	0/72 (0.0)	10/285 (3.5)	1/144 (0.7)
RR [95%-CI]; p-value	3.57 [0.45, 28.50], 0.2291		3.02 [0.15, 59.51], 0.4672		5.05 [0.65, 39.09], 0.1207	
OR [95%-CI]; p-value	3.71 [0.45, 30.74], 0.1942		3.06 [0.15, 61.99], 0.4428		5.20 [0.66, 41.03], 0.0816	
RD [95%-CI]; p-value	0.04 [-0.01, 0.08], 0.1186		0.01 [-0.02, 0.04], 0.3644		0.03 [0.00, 0.05], 0.0293	
heterogeneity (RR)						
p-value					0.9276	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9188	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq.sas using SAS 9.4

Table 12.4.4.1.7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
n/N (%)	12/141 (8.5)	9/72 (12.5)	13/144 (9.0)	6/72 (8.3)	25/285 (8.8)	15/144 (10.4)
RR [95%-CI]; p-value	0.68 [0.30, 1.54], 0.3560		1.08 [0.43, 2.73], 0.8653		0.84 [0.46, 1.55], 0.5796	
OR [95%-CI]; p-value	0.65 [0.26, 1.63], 0.3556		1.09 [0.40, 3.00], 0.8651		0.83 [0.42, 1.62], 0.5801	
RD [95%-CI]; p-value	-0.04 [-0.13, 0.05], 0.3807		0.01 [-0.07, 0.09], 0.8635		-0.02 [-0.08, 0.04], 0.5894	
heterogeneity (RR)						
p-value					0.4606	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4568	
Number of Patients with Any Severe SMQ of Cardiac Failure						
n/N (%)	2/141 (1.4)	0/72 (0.0)	4/144 (2.8)	1/72 (1.4)	6/285 (2.1)	1/144 (0.7)
RR [95%-CI]; p-value	2.06 [0.09, 45.02], 0.6470		2.00 [0.23, 17.57], 0.5318		3.03 [0.37, 24.94], 0.3023	
OR [95%-CI]; p-value	2.07 [0.09, 46.55], 0.6392		2.03 [0.22, 18.49], 0.5222		3.08 [0.37, 25.79], 0.2761	
RD [95%-CI]; p-value	0.01 [-0.02, 0.03], 0.6005		0.01 [-0.02, 0.05], 0.4749		0.01 [-0.01, 0.04], 0.1982	
heterogeneity (RR)						
p-value					0.9884	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9913	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq.sas using SAS 9.4

Table 12.4.4.1.7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
n/N (%)	10/141 (7.1)	9/72 (12.5)	10/144 (6.9)	6/72 (8.3)	20/285 (7.0)	15/144 (10.4)
RR [95%-CI]; p-value	0.57 [0.24, 1.33], 0.1937		0.83 [0.32, 2.20], 0.7131		0.67 [0.36, 1.28], 0.2255	
OR [95%-CI]; p-value	0.53 [0.21, 1.38], 0.1903		0.82 [0.29, 2.36], 0.7133		0.65 [0.32, 1.31], 0.2245	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.03], 0.2250		-0.01 [-0.09, 0.06], 0.7208		-0.03 [-0.09, 0.02], 0.2510	
heterogeneity (RR)						
p-value					0.5604	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5524	
Number of Patients with Any Serious SMQ of Cardiac Failure						
n/N (%)	5/141 (3.5)	0/72 (0.0)	5/144 (3.5)	1/72 (1.4)	10/285 (3.5)	1/144 (0.7)
RR [95%-CI]; p-value	5.14 [0.28, 92.82], 0.2673		2.50 [0.30, 21.00], 0.3988		5.05 [0.65, 39.09], 0.1207	
OR [95%-CI]; p-value	5.29 [0.29, 98.27], 0.2122		2.55 [0.29, 22.28], 0.3798		5.20 [0.66, 41.03], 0.0816	
RD [95%-CI]; p-value	0.03 [-0.01, 0.06], 0.1197		0.02 [-0.02, 0.06], 0.3111		0.03 [0.00, 0.05], 0.0293	
heterogeneity (RR)						
p-value					0.6939	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6903	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq.sas using SAS 9.4

Table 12.4.4.1.6
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
n/N (%)	24/141 (17.0)	18/72 (25.0)	28/144 (19.4)	9/72 (12.5)	52/285 (18.2)	27/144 (18.8)
RR [95%-CI]; p-value	0.68 [0.40, 1.17], 0.1639		1.56 [0.78, 3.12], 0.2132		0.97 [0.64, 1.48], 0.8986	
OR [95%-CI]; p-value	0.62 [0.31, 1.23], 0.1662		1.69 [0.75, 3.80], 0.2016		0.97 [0.58, 1.62], 0.8987	
RD [95%-CI]; p-value	-0.08 [-0.20, 0.04], 0.1839		0.07 [-0.03, 0.17], 0.1738		-0.01 [-0.08, 0.07], 0.8991	
heterogeneity (RR)						
p-value					0.0662	
I^2					70.4%	
heterogeneity (OR)						
p-value					0.0610	
Number of Patients with Any Severe ADR						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
RR [95%-CI]; p-value	1.03 [0.03, 30.29], 0.9871		NA		1.01 [0.03, 30.05], 0.9936	
OR [95%-CI]; p-value	1.03 [0.03, 31.03], 0.9871		NA		1.01 [0.03, 30.41], 0.9936	
RD [95%-CI]; p-value	0.00 [-0.02, 0.02], 0.9870		NA		0.00 [-0.01, 0.01], 0.9936	
heterogeneity (RR)						
p-value					0.7856	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.7844	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_6_m_pt_adr.sas using SAS 9.4

Table 12.4.4.1.6
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe ADR						
n/N (%)	23/141 (16.3)	18/72 (25.0)	28/144 (19.4)	9/72 (12.5)	51/285 (17.9)	27/144 (18.8)
RR [95%-CI]; p-value	0.65 [0.38, 1.13], 0.1264		1.56 [0.78, 3.12], 0.2132		0.95 [0.63, 1.45], 0.8280	
OR [95%-CI]; p-value	0.58 [0.29, 1.17], 0.1282		1.69 [0.75, 3.80], 0.2016		0.94 [0.56, 1.58], 0.8283	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.03], 0.1461		0.07 [-0.03, 0.17], 0.1738		-0.01 [-0.09, 0.07], 0.8293	
heterogeneity (RR)						
p-value					0.0544	
I^2					73.0%	
heterogeneity (OR)						
p-value					0.0496	
Number of Patients with Any Serious ADR						
n/N (%)	2/141 (1.4)	0/72 (0.0)	1/144 (0.7)	1/72 (1.4)	3/285 (1.1)	1/144 (0.7)
RR [95%-CI]; p-value	2.06 [0.09, 45.02], 0.6470		0.50 [0.03, 7.88], 0.6222		1.52 [0.16, 14.44], 0.7176	
OR [95%-CI]; p-value	2.07 [0.09, 46.55], 0.6392		0.50 [0.03, 8.05], 0.6154		1.52 [0.16, 14.76], 0.7155	
RD [95%-CI]; p-value	0.01 [-0.02, 0.03], 0.6005		-0.01 [-0.04, 0.02], 0.6527		0.00 [-0.01, 0.02], 0.6967	
heterogeneity (RR)						
p-value					0.5030	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4910	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_6_m_pt_adr.sas using SAS 9.4

Table 12.4.9.1.1
Summary of TEAE Leading to Study Discontinuation by SOC
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE leading to death						
n/N (%)	3/141 (2.1)	1/72 (1.4)	3/144 (2.1)	1/72 (1.4)	6/285 (2.1)	2/144 (1.4)
Number of Patients with AE leading to treatment discontinuation						
n/N (%)	16/141 (11.3)	5/72 (6.9)	15/144 (10.4)	4/72 (5.6)	31/285 (10.9)	9/144 (6.3)
Number of Patients with AE leading to study discontinuation						
n/N (%)	8/141 (5.7)	2/72 (2.8)	7/144 (4.9)	3/72 (4.2)	15/285 (5.3)	5/144 (3.5)
Blood and lymphatic system disorders						
n/N (%)	0/141 (0.0)	0/72 (0.0)	0/144 (0.0)	1/72 (1.4)	0/285 (0.0)	1/144 (0.7)
Cardiac disorders						
n/N (%)	2/141 (1.4)	0/72 (0.0)	1/144 (0.7)	1/72 (1.4)	3/285 (1.1)	1/144 (0.7)
Gastrointestinal disorders						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.1
Summary of TEAE Leading to Study Discontinuation by SOC
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
n/N (%)	3/141 (2.1)	0/72 (0.0)	0/144 (0.0)	1/72 (1.4)	3/285 (1.1)	1/144 (0.7)
Injury, poisoning and procedural complications						
n/N (%)	2/141 (1.4)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	3/285 (1.1)	0/144 (0.0)
Investigations						
n/N (%)	1/141 (0.7)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	2/285 (0.7)	0/144 (0.0)
Metabolism and nutrition disorders						
n/N (%)	2/141 (1.4)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	2/285 (0.7)	0/144 (0.0)
Musculoskeletal and connective tissue disorders						
n/N (%)	1/141 (0.7)	1/72 (1.4)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	1/144 (0.7)
Nervous system disorders						
n/N (%)	0/141 (0.0)	1/72 (1.4)	2/144 (1.4)	0/72 (0.0)	2/285 (0.7)	1/144 (0.7)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.1
Summary of TEAE Leading to Study Discontinuation by SOC
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Psychiatric disorders						
n/N (%)	0/141 (0.0)	1/72 (1.4)	0/144 (0.0)	0/72 (0.0)	0/285 (0.0)	1/144 (0.7)
Respiratory, thoracic and mediastinal disorders						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE leading to death						
n/N (%)	3/141 (2.1)	1/72 (1.4)	3/144 (2.1)	1/72 (1.4)	6/285 (2.1)	2/144 (1.4)
Number of Patients with AE leading to treatment discontinuation						
n/N (%)	16/141 (11.3)	5/72 (6.9)	15/144 (10.4)	4/72 (5.6)	31/285 (10.9)	9/144 (6.3)
Number of Patients with AE leading to study discontinuation						
n/N (%)	8/141 (5.7)	2/72 (2.8)	7/144 (4.9)	3/72 (4.2)	15/285 (5.3)	5/144 (3.5)
Blood and lymphatic system disorders						
Anaemia						
n/N (%)	0/141 (0.0)	0/72 (0.0)	0/144 (0.0)	1/72 (1.4)	0/285 (0.0)	1/144 (0.7)
Cardiac disorders						
Acute myocardial infarction						
n/N (%)	0/141 (0.0)	0/72 (0.0)	0/144 (0.0)	1/72 (1.4)	0/285 (0.0)	1/144 (0.7)
Cardiac arrest						
n/N (%)	1/141 (0.7)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	2/285 (0.7)	0/144 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac failure congestive						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Gastrointestinal disorders						
Nausea						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Infections and infestations						
Pneumonia						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Sepsis						
n/N (%)	0/141 (0.0)	0/72 (0.0)	0/144 (0.0)	1/72 (1.4)	0/285 (0.0)	1/144 (0.7)
Urosepsis						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Wound infection						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Fall						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Multiple fractures						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Wound						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Investigations						
Blood creatinine increased						
n/N (%)	1/141 (0.7)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	2/285 (0.7)	0/144 (0.0)
Metabolism and nutrition disorders						
Fluid overload						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Hypercalcaemia						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Arthralgia						
n/N (%)	1/141 (0.7)	0/72 (0.0)	0/144 (0.0)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Muscular weakness						
n/N (%)	0/141 (0.0)	1/72 (1.4)	0/144 (0.0)	0/72 (0.0)	0/285 (0.0)	1/144 (0.7)
Nervous system disorders						
Amnesia						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Cerebrovascular accident						
n/N (%)	0/141 (0.0)	1/72 (1.4)	0/144 (0.0)	0/72 (0.0)	0/285 (0.0)	1/144 (0.7)
Myasthenia gravis crisis						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)
Psychiatric disorders						
Hallucination						
n/N (%)	0/141 (0.0)	1/72 (1.4)	0/144 (0.0)	0/72 (0.0)	0/285 (0.0)	1/144 (0.7)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Epistaxis						
n/N (%)	0/141 (0.0)	0/72 (0.0)	1/144 (0.7)	0/72 (0.0)	1/285 (0.4)	0/144 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Nachberechnungsdokument Sicherheitsendpunkte Unerwünschte Ereignisse (PP-Population)

Folgende Daten werden für die PP-Population dargestellt:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (SMQs)
  - UE ohne erkrankungsbezogene Ereignisse
  - UE nach SOC, die zum Abbruch führten
  - UE nach PT, die zum Abbruch führten

Table 12.4.3.1.s10
Overall Summary of Treatment-Emmergent Adverse Events
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with AE						
n/N (%)	83/115 (72.2)	50/62 (80.6)	72/119 (60.5)	37/60 (61.7)	155/234 (66.2)	87/122 (71.3)
RR [95%-CI]; p-value	0.89 [0.76, 1.06], 0.1916		0.98 [0.77, 1.26], 0.8798		0.93 [0.80, 1.07], 0.3187	
OR [95%-CI]; p-value	0.62 [0.29, 1.32], 0.2135		0.95 [0.50, 1.80], 0.8804		0.79 [0.49, 1.27], 0.3303	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1945		-0.01 [-0.16, 0.14], 0.8802		-0.05 [-0.15, 0.05], 0.3229	
heterogeneity (RR)						
p-value					0.5449	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3968	
Number of patients with drug-related AE						
n/N (%)	13/115 (11.3)	10/62 (16.1)	13/119 (10.9)	2/60 (3.3)	26/234 (11.1)	12/122 (9.8)
RR [95%-CI]; p-value	0.70 [0.33, 1.51], 0.3621		3.28 [0.76, 14.06], 0.1101		1.13 [0.59, 2.16], 0.7124	
OR [95%-CI]; p-value	0.66 [0.27, 1.61], 0.3625		3.56 [0.78, 16.31], 0.0836		1.15 [0.56, 2.36], 0.7116	
RD [95%-CI]; p-value	-0.05 [-0.16, 0.06], 0.3826		0.08 [0.00, 0.15], 0.0392		0.01 [-0.05, 0.08], 0.7068	
heterogeneity (RR)						
p-value					0.0660	
I^2					70.4%	
heterogeneity (OR)						
p-value					0.0506	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1.s10
Overall Summary of Treatment-Emmergent Adverse Events
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with severe AE						
n/N (%)	12/115 (10.4)	4/62 (6.5)	3/119 (2.5)	5/60 (8.3)	15/234 (6.4)	9/122 (7.4)
RR [95%-CI]; p-value	1.62 [0.54, 4.80], 0.3867		0.30 [0.07, 1.22], 0.0935		0.87 [0.39, 1.93], 0.7297	
OR [95%-CI]; p-value	1.69 [0.52, 5.48], 0.3780		0.28 [0.07, 1.23], 0.0756		0.86 [0.36, 2.03], 0.7299	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3459		-0.06 [-0.13, 0.02], 0.1308		-0.01 [-0.07, 0.05], 0.7351	
heterogeneity (RR)						
p-value					0.0636	
I^2					70.9%	
heterogeneity (OR)						
p-value					0.0545	
Number of Patients with SAE						
n/N (%)	20/115 (17.4)	10/62 (16.1)	12/119 (10.1)	7/60 (11.7)	32/234 (13.7)	17/122 (13.9)
RR [95%-CI]; p-value	1.08 [0.54, 2.16], 0.8313		0.86 [0.36, 2.08], 0.7451		0.98 [0.57, 1.69], 0.9463	
OR [95%-CI]; p-value	1.09 [0.48, 2.51], 0.8309		0.85 [0.32, 2.28], 0.7456		0.98 [0.52, 1.84], 0.9463	
RD [95%-CI]; p-value	0.01 [-0.10, 0.13], 0.8294		-0.02 [-0.11, 0.08], 0.7506		-0.00 [-0.08, 0.07], 0.9464	
heterogeneity (RR)						
p-value					0.6987	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6996	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1.s10
Overall Summary of Treatment-Emmergent Adverse Events
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with AE leading to treatment discontiuation						
n/N (%)	8/115 (7.0)	3/62 (4.8)	5/119 (4.2)	0/60 (0.0)	13/234 (5.6)	3/122 (2.5)
RR [95%-CI]; p-value	1.44 [0.40, 5.23], 0.5814		5.08 [0.28, 91.53], 0.2702		2.26 [0.66, 7.78], 0.1963	
OR [95%-CI]; p-value	1.47 [0.38, 5.75], 0.5777		5.26 [0.28, 97.96], 0.2149		2.33 [0.65, 8.35], 0.1808	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5578		0.03 [-0.01, 0.08], 0.1210		0.03 [-0.01, 0.07], 0.1312	
heterogeneity (RR)						
p-value					0.4342	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4179	
Number of Patients with AE leading to study discontinuation						
n/N (%)	1/115 (0.9)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	1/122 (0.8)
RR [95%-CI]; p-value	0.54 [0.03, 8.47], 0.6602		0.51 [0.01, 25.20], 0.7328		0.52 [0.03, 8.26], 0.6441	
OR [95%-CI]; p-value	0.54 [0.03, 8.70], 0.6553		0.50 [0.01, 25.72], 0.7279		0.52 [0.03, 8.37], 0.6383	
RD [95%-CI]; p-value	-0.01 [-0.04, 0.03], 0.6828		-0.00 [-0.03, 0.02], 0.7546		-0.00 [-0.02, 0.01], 0.6701	
heterogeneity (RR)						
p-value					0.9794	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9807	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1.s10
Overall Summary of Treatment-Emmergent Adverse Events
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with AE leading to death						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)
RR [95%-CI]; p-value	0.27 [0.01, 7.89], 0.4457		0.51 [0.01, 25.20], 0.7328		0.26 [0.01, 7.70], 0.4359	
OR [95%-CI]; p-value	0.27 [0.01, 8.02], 0.4129		0.50 [0.01, 25.72], 0.7279		0.26 [0.01, 7.76], 0.4013	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.02], 0.4908		-0.00 [-0.03, 0.02], 0.7546		-0.01 [-0.02, 0.01], 0.4858	
heterogeneity (RR)						
p-value					0.8098	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8079	
Number of Patients with AE by severity						
Mild						
n/N (%)	68/115 (59.1)	45/62 (72.6)	60/119 (50.4)	29/60 (48.3)	128/234 (54.7)	74/122 (60.7)
RR* [95%-CI]; p-value	0.81 [0.66, 1.01], 0.0625		1.04 [0.76, 1.43], 0.7935		0.90 [0.75, 1.08], 0.2722	
OR* [95%-CI]; p-value	0.55 [0.28, 1.07], 0.0756		1.09 [0.58, 2.02], 0.7921		0.78 [0.50, 1.22], 0.2818	
RD* [95%-CI]; p-value	-0.13 [-0.28, 0.01], 0.0650		0.02 [-0.13, 0.18], 0.7920		-0.06 [-0.17, 0.05], 0.2781	
heterogeneity (RR)						
p-value					0.2058	
I^2					37.5%	
heterogeneity (OR)						
p-value					0.1395	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.3.1.s10
Overall Summary of Treatment-Emmergent Adverse Events
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
n/N (%)	38/115 (33.0)	25/62 (40.3)	36/119 (30.3)	16/60 (26.7)	74/234 (31.6)	41/122 (33.6)
RR* [95%-CI]; p-value	0.82 [0.55, 1.22], 0.3284		1.13 [0.69, 1.87], 0.6213		0.94 [0.69, 1.29], 0.7030	
OR* [95%-CI]; p-value	0.73 [0.39, 1.38], 0.3346		1.19 [0.60, 2.39], 0.6179		0.91 [0.57, 1.46], 0.7042	
RD* [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3394		0.04 [-0.10, 0.17], 0.6133		-0.02 [-0.12, 0.08], 0.7055	
heterogeneity (RR)						
p-value					0.3194	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3074	
Severe						
n/N (%)	12/115 (10.4)	4/62 (6.5)	3/119 (2.5)	5/60 (8.3)	15/234 (6.4)	9/122 (7.4)
RR* [95%-CI]; p-value	1.62 [0.54, 4.80], 0.3867		0.30 [0.07, 1.22], 0.0935		0.87 [0.39, 1.93], 0.7297	
OR* [95%-CI]; p-value	1.69 [0.52, 5.48], 0.3780		0.28 [0.07, 1.23], 0.0756		0.86 [0.36, 2.03], 0.7299	
RD* [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3459		-0.06 [-0.13, 0.02], 0.1308		-0.01 [-0.07, 0.05], 0.7351	
heterogeneity (RR)						
p-value					0.0636	
I^2					70.9%	
heterogeneity (OR)						
p-value					0.0545	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
n/N (%)	8/115 (7.0)	9/62 (14.5)	7/119 (5.9)	2/60 (3.3)	15/234 (6.4)	11/122 (9.0)
RR [95%-CI]; p-value	0.48 [0.19, 1.18], 0.1095		1.76 [0.38, 8.24], 0.4699		0.71 [0.34, 1.50], 0.3705	
OR [95%-CI]; p-value	0.44 [0.16, 1.21], 0.1035		1.81 [0.36, 9.01], 0.4613		0.69 [0.31, 1.55], 0.3697	
RD [95%-CI]; p-value	-0.08 [-0.17, 0.02], 0.1355		0.03 [-0.04, 0.09], 0.4207		-0.03 [-0.09, 0.03], 0.3925	
heterogeneity (RR)						
p-value					0.1522	
I^2					51.2%	
heterogeneity (OR)						
p-value					0.1321	
Gastrointestinal disorders						
n/N (%)	21/115 (18.3)	18/62 (29.0)	23/119 (19.3)	6/60 (10.0)	44/234 (18.8)	24/122 (19.7)
RR [95%-CI]; p-value	0.63 [0.36, 1.09], 0.0976		1.93 [0.83, 4.49], 0.1256		0.96 [0.61, 1.49], 0.8429	
OR [95%-CI]; p-value	0.55 [0.26, 1.13], 0.0991		2.16 [0.83, 5.62], 0.1099		0.95 [0.54, 1.65], 0.8431	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1131		0.09 [-0.01, 0.20], 0.0785		-0.01 [-0.10, 0.08], 0.8440	
heterogeneity (RR)						
p-value					0.0287	
I^2					79.1%	
heterogeneity (OR)						
p-value					0.0226	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; RD: PP: Per-Protocol; Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
n/N (%)	15/115 (13.0)	15/62 (24.2)	14/119 (11.8)	7/60 (11.7)	29/234 (12.4)	22/122 (18.0)
RR [95%-CI]; p-value	0.54 [0.28, 1.03], 0.0607		1.01 [0.43, 2.37], 0.9847		0.69 [0.41, 1.14], 0.1488	
OR [95%-CI]; p-value	0.47 [0.21, 1.04], 0.0593		1.01 [0.38, 2.65], 0.9846		0.64 [0.35, 1.18], 0.1494	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.01], 0.0758		0.00 [-0.10, 0.10], 0.9846		-0.06 [-0.14, 0.02], 0.1683	
heterogeneity (RR)						
p-value					0.2511	
I^2					24.1%	
heterogeneity (OR)						
p-value					0.2288	
Infections and infestations						
n/N (%)	31/115 (27.0)	17/62 (27.4)	28/119 (23.5)	14/60 (23.3)	59/234 (25.2)	31/122 (25.4)
RR [95%-CI]; p-value	0.98 [0.59, 1.63], 0.9473		1.01 [0.58, 1.77], 0.9767		0.99 [0.68, 1.44], 0.9677	
OR [95%-CI]; p-value	0.98 [0.49, 1.95], 0.9473		1.01 [0.49, 2.10], 0.9767		0.99 [0.60, 1.64], 0.9678	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9474		0.00 [-0.13, 0.13], 0.9767		-0.00 [-0.10, 0.09], 0.9678	
heterogeneity (RR)						
p-value					0.9474	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9469	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; RD: PP: Per-Protocol; Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
n/N (%)	14/115 (12.2)	10/62 (16.1)	11/119 (9.2)	5/60 (8.3)	25/234 (10.7)	15/122 (12.3)
RR [95%-CI]; p-value	0.75 [0.36, 1.60], 0.4625		1.11 [0.40, 3.05], 0.8406		0.87 [0.48, 1.59], 0.6472	
OR [95%-CI]; p-value	0.72 [0.30, 1.73], 0.4634		1.12 [0.37, 3.39], 0.8403		0.85 [0.43, 1.69], 0.6477	
RD [95%-CI]; p-value	-0.04 [-0.15, 0.07], 0.4783		0.01 [-0.08, 0.10], 0.8378		-0.02 [-0.09, 0.05], 0.6539	
heterogeneity (RR)						
p-value					0.5488	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5396	
Metabolism and nutrition disorders						
n/N (%)	23/115 (20.0)	19/62 (30.6)	21/119 (17.6)	12/60 (20.0)	44/234 (18.8)	31/122 (25.4)
RR [95%-CI]; p-value	0.65 [0.39, 1.10], 0.1100		0.88 [0.47, 1.67], 0.7005		0.74 [0.49, 1.11], 0.1442	
OR [95%-CI]; p-value	0.57 [0.28, 1.15], 0.1123		0.86 [0.39, 1.89], 0.7016		0.68 [0.40, 1.15], 0.1468	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1252		-0.02 [-0.15, 0.10], 0.7059		-0.07 [-0.16, 0.03], 0.1596	
heterogeneity (RR)						
p-value					0.4737	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4418	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; RD: PP: Per-Protocol; Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
n/N (%)	20/115 (17.4)	20/62 (32.3)	20/119 (16.8)	14/60 (23.3)	40/234 (17.1)	34/122 (27.9)
RR [95%-CI]; p-value	0.54 [0.31, 0.92], 0.0242		0.72 [0.39, 1.32], 0.2905		0.61 [0.41, 0.92], 0.0170	
OR [95%-CI]; p-value	0.44 [0.22, 0.91], 0.0241		0.66 [0.31, 1.43], 0.2933		0.53 [0.32, 0.90], 0.0174	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.01], 0.0314		-0.07 [-0.19, 0.06], 0.3114		-0.11 [-0.20, -0.01], 0.0232	
heterogeneity (RR)						
p-value					0.4843	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4482	
Nervous system disorders						
n/N (%)	11/115 (9.6)	11/62 (17.7)	13/119 (10.9)	7/60 (11.7)	24/234 (10.3)	18/122 (14.8)
RR [95%-CI]; p-value	0.54 [0.25, 1.17], 0.1189		0.94 [0.39, 2.22], 0.8816		0.70 [0.39, 1.23], 0.2117	
OR [95%-CI]; p-value	0.49 [0.20, 1.21], 0.1157		0.93 [0.35, 2.46], 0.8817		0.66 [0.34, 1.27], 0.2118	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1423		-0.01 [-0.11, 0.09], 0.8828		-0.04 [-0.12, 0.03], 0.2334	
heterogeneity (RR)						
p-value					0.3519	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3446	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; RD: PP: Per-Protocol; Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
n/N (%)	4/115 (3.5)	7/62 (11.3)	5/119 (4.2)	2/60 (3.3)	9/234 (3.8)	9/122 (7.4)
RR [95%-CI]; p-value	0.31 [0.09, 1.01], 0.0523		1.26 [0.25, 6.31], 0.7781		0.52 [0.21, 1.28], 0.1550	
OR [95%-CI]; p-value	0.28 [0.08, 1.01], 0.0400		1.27 [0.24, 6.76], 0.7772		0.50 [0.19, 1.30], 0.1490	
RD [95%-CI]; p-value	-0.08 [-0.16, 0.01], 0.0737		0.01 [-0.05, 0.07], 0.7691		-0.04 [-0.09, 0.02], 0.1876	
heterogeneity (RR)						
p-value					0.1677	
I^2					47.5%	
heterogeneity (OR)						
p-value					0.1505	
Respiratory, thoracic and mediastinal disorders						
n/N (%)	15/115 (13.0)	10/62 (16.1)	13/119 (10.9)	5/60 (8.3)	28/234 (12.0)	15/122 (12.3)
RR [95%-CI]; p-value	0.81 [0.39, 1.69], 0.5729		1.31 [0.49, 3.51], 0.5896		0.97 [0.54, 1.75], 0.9279	
OR [95%-CI]; p-value	0.78 [0.33, 1.86], 0.5739		1.35 [0.46, 3.98], 0.5864		0.97 [0.50, 1.89], 0.9279	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.5836		0.03 [-0.06, 0.12], 0.5710		-0.00 [-0.07, 0.07], 0.9282	
heterogeneity (RR)						
p-value					0.4414	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4372	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; RD: PP: Per-Protocol; Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.1.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
n/N (%)	6/115 (5.2)	8/62 (12.9)	12/119 (10.1)	6/60 (10.0)	18/234 (7.7)	14/122 (11.5)
RR [95%-CI]; p-value	0.40 [0.15, 1.11], 0.0796		1.01 [0.40, 2.55], 0.9859		0.67 [0.35, 1.30], 0.2372	
OR [95%-CI]; p-value	0.37 [0.12, 1.12], 0.0707		1.01 [0.36, 2.84], 0.9859		0.64 [0.31, 1.34], 0.2362	
RD [95%-CI]; p-value	-0.08 [-0.17, 0.02], 0.1046		0.00 [-0.09, 0.09], 0.9859		-0.04 [-0.10, 0.03], 0.2617	
heterogeneity (RR)						
p-value					0.1925	
I^2					41.1%	
heterogeneity (OR)						
p-value					0.1923	
Vascular disorders						
n/N (%)	12/115 (10.4)	8/62 (12.9)	6/119 (5.0)	7/60 (11.7)	18/234 (7.7)	15/122 (12.3)
RR [95%-CI]; p-value	0.81 [0.35, 1.87], 0.6201		0.43 [0.15, 1.23], 0.1157		0.63 [0.33, 1.20], 0.1569	
OR [95%-CI]; p-value	0.79 [0.30, 2.04], 0.6207		0.40 [0.13, 1.25], 0.1069		0.59 [0.29, 1.23], 0.1552	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.08], 0.6300		-0.07 [-0.16, 0.02], 0.1502		-0.05 [-0.11, 0.02], 0.1816	
heterogeneity (RR)						
p-value					0.3597	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3738	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; RD: PP: Per-Protocol; Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.3.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by PT

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
n/N (%)	4/115 (3.5)	12/62 (19.4)	6/119 (5.0)	0/60 (0.0)	10/234 (4.3)	12/122 (9.8)
RR [95%-CI]; p-value	0.18 [0.06, 0.53], 0.0020		6.10 [0.35, 107.42], 0.2166		0.43 [0.19, 0.98], 0.0437	
OR [95%-CI]; p-value	0.15 [0.05, 0.49], 0.0004		6.37 [0.35, 116.02], 0.1530		0.41 [0.17, 0.98], 0.0386	
RD [95%-CI]; p-value	-0.16 [-0.26, -0.05], 0.0027		0.04 [-0.00, 0.09], 0.0691		-0.06 [-0.11, 0.00], 0.0640	
heterogeneity (RR)						
p-value					0.0243	
I^2					80.3%	
heterogeneity (OR)						
p-value					0.0028	
Infections and infestations						
Urinary tract infection						
n/N (%)	4/115 (3.5)	8/62 (12.9)	7/119 (5.9)	2/60 (3.3)	11/234 (4.7)	10/122 (8.2)
RR [95%-CI]; p-value	0.27 [0.08, 0.86], 0.0267		1.76 [0.38, 8.24], 0.4699		0.57 [0.25, 1.31], 0.1881	
OR [95%-CI]; p-value	0.24 [0.07, 0.84], 0.0173		1.81 [0.36, 9.01], 0.4613		0.55 [0.23, 1.34], 0.1839	
RD [95%-CI]; p-value	-0.09 [-0.18, -0.00], 0.0399		0.03 [-0.04, 0.09], 0.4207		-0.03 [-0.09, 0.02], 0.2188	
heterogeneity (RR)						
p-value					0.0562	
I^2					72.6%	
heterogeneity (OR)						
p-value					0.0433	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_3_m_pt_ae10pct_pp.sas using SAS 9.4

Table 12.4.4.1.3.s10

Summary of TEAE (independent of severity) Occurring≥ 10% in One Arm by PT

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
n/N (%)	8/115 (7.0)	4/62 (6.5)	4/119 (3.4)	6/60 (10.0)	12/234 (5.1)	10/122 (8.2)
RR [95%-CI]; p-value	1.08 [0.34, 3.44], 0.8987		0.34 [0.10, 1.15], 0.0815		0.63 [0.28, 1.41], 0.2566	
OR [95%-CI]; p-value	1.08 [0.31, 3.75], 0.8986		0.31 [0.08, 1.16], 0.0679		0.61 [0.25, 1.44], 0.2538	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8975		-0.07 [-0.15, 0.02], 0.1149		-0.03 [-0.09, 0.03], 0.2853	
heterogeneity (RR)						
p-value					0.1759	
I^2					45.4%	
heterogeneity (OR)						
p-value					0.1708	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_3_m_pt_ae10pct_pp.sas using SAS 9.4

Table 12.4.8.1.1.s10

Summary of SAE Occurring ≥ 5% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
n/N (%)	2/115 (1.7)	1/62 (1.6)	2/119 (1.7)	3/60 (5.0)	4/234 (1.7)	4/122 (3.3)
RR [95%-CI]; p-value	1.08 [0.10, 11.66], 0.9505		0.34 [0.06, 1.96], 0.2253		0.52 [0.13, 2.05], 0.3509	
OR [95%-CI]; p-value	1.08 [0.10, 12.15], 0.9505		0.32 [0.05, 2.00], 0.2033		0.51 [0.13, 2.09], 0.3430	
RD [95%-CI]; p-value	0.00 [-0.04, 0.04], 0.9500		-0.03 [-0.09, 0.03], 0.2765		-0.02 [-0.05, 0.02], 0.3889	
heterogeneity (RR)						
p-value					0.4405	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4288	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.8.1.2.s10

Summary of SAE Occurring ≥ 5% in One Arm by PT

PP Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.5.1.1.s10

Summary of Severe TEAE Occurring ≥ 5% in One Arm by SOC

PP Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.5.1.2.s10

Summary of Severe TEAE Occurring ≥ 5% in One Arm by PT

PP Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.

TEAE: Treatment emergent adverse event; SOC: System Organ Class; RR: Relative Risk; OR: Odds Ratio; RD: Risk Difference.

N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.2.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
n/N (%)	21/115 (18.3)	18/62 (29.0)	23/119 (19.3)	6/60 (10.0)	44/234 (18.8)	24/122 (19.7)
RR [95%-CI]; p-value	0.63 [0.36, 1.09], 0.0976		1.93 [0.83, 4.49], 0.1256		0.96 [0.61, 1.49], 0.8429	
OR [95%-CI]; p-value	0.55 [0.26, 1.13], 0.0991		2.16 [0.83, 5.62], 0.1099		0.95 [0.54, 1.65], 0.8431	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1131		0.09 [-0.01, 0.20], 0.0785		-0.01 [-0.10, 0.08], 0.8440	
heterogeneity (RR)						
p-value					0.0287	
I^2					79.1%	
heterogeneity (OR)						
p-value					0.0226	
General disorders and administration site conditions						
n/N (%)	15/115 (13.0)	15/62 (24.2)	14/119 (11.8)	7/60 (11.7)	29/234 (12.4)	22/122 (18.0)
RR [95%-CI]; p-value	0.54 [0.28, 1.03], 0.0607		1.01 [0.43, 2.37], 0.9847		0.69 [0.41, 1.14], 0.1488	
OR [95%-CI]; p-value	0.47 [0.21, 1.04], 0.0593		1.01 [0.38, 2.65], 0.9846		0.64 [0.35, 1.18], 0.1494	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.01], 0.0758		0.00 [-0.10, 0.10], 0.9846		-0.06 [-0.14, 0.02], 0.1683	
heterogeneity (RR)						
p-value					0.2511	
I^2					24.1%	
heterogeneity (OR)						
p-value					0.2288	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_2_m_soc_ae1pct_pp.sas using SAS 9.4

Table 12.4.4.1.2.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
n/N (%)	31/115 (27.0)	17/62 (27.4)	28/119 (23.5)	14/60 (23.3)	59/234 (25.2)	31/122 (25.4)
RR [95%-CI]; p-value	0.98 [0.59, 1.63], 0.9473		1.01 [0.58, 1.77], 0.9767		0.99 [0.68, 1.44], 0.9677	
OR [95%-CI]; p-value	0.98 [0.49, 1.95], 0.9473		1.01 [0.49, 2.10], 0.9767		0.99 [0.60, 1.64], 0.9678	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9474		0.00 [-0.13, 0.13], 0.9767		-0.00 [-0.10, 0.09], 0.9678	
heterogeneity (RR)						
p-value					0.9474	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9469	
Injury, poisoning and procedural complications						
n/N (%)	11/115 (9.6)	5/62 (8.1)	8/119 (6.7)	2/60 (3.3)	19/234 (8.1)	7/122 (5.7)
RR [95%-CI]; p-value	1.19 [0.43, 3.26], 0.7408		2.02 [0.44, 9.20], 0.3651		1.42 [0.61, 3.27], 0.4170	
OR [95%-CI]; p-value	1.21 [0.40, 3.64], 0.7398		2.09 [0.43, 10.16], 0.3513		1.45 [0.59, 3.56], 0.4123	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.7338		0.03 [-0.03, 0.10], 0.2988		0.02 [-0.03, 0.08], 0.3882	
heterogeneity (RR)						
p-value					0.5684	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5743	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_2_m_soc_ae1pct_pp.sas using SAS 9.4

Table 12.4.4.1.2.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
n/N (%)	14/115 (12.2)	10/62 (16.1)	11/119 (9.2)	5/60 (8.3)	25/234 (10.7)	15/122 (12.3)
RR [95%-CI]; p-value	0.75 [0.36, 1.60], 0.4625		1.11 [0.40, 3.05], 0.8406		0.87 [0.48, 1.59], 0.6472	
OR [95%-CI]; p-value	0.72 [0.30, 1.73], 0.4634		1.12 [0.37, 3.39], 0.8403		0.85 [0.43, 1.69], 0.6477	
RD [95%-CI]; p-value	-0.04 [-0.15, 0.07], 0.4783		0.01 [-0.08, 0.10], 0.8378		-0.02 [-0.09, 0.05], 0.6539	
heterogeneity (RR)						
p-value					0.5488	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5396	
Metabolism and nutrition disorders						
n/N (%)	23/115 (20.0)	19/62 (30.6)	21/119 (17.6)	12/60 (20.0)	44/234 (18.8)	31/122 (25.4)
RR [95%-CI]; p-value	0.65 [0.39, 1.10], 0.1100		0.88 [0.47, 1.67], 0.7005		0.74 [0.49, 1.11], 0.1442	
OR [95%-CI]; p-value	0.57 [0.28, 1.15], 0.1123		0.86 [0.39, 1.89], 0.7016		0.68 [0.40, 1.15], 0.1468	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1252		-0.02 [-0.15, 0.10], 0.7059		-0.07 [-0.16, 0.03], 0.1596	
heterogeneity (RR)						
p-value					0.4737	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4418	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_2_m_soc_ae1pct_pp.sas using SAS 9.4

Table 12.4.4.1.2.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
n/N (%)	20/115 (17.4)	20/62 (32.3)	20/119 (16.8)	14/60 (23.3)	40/234 (17.1)	34/122 (27.9)
RR [95%-CI]; p-value	0.54 [0.31, 0.92], 0.0242		0.72 [0.39, 1.32], 0.2905		0.61 [0.41, 0.92], 0.0170	
OR [95%-CI]; p-value	0.44 [0.22, 0.91], 0.0241		0.66 [0.31, 1.43], 0.2933		0.53 [0.32, 0.90], 0.0174	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.01], 0.0314		-0.07 [-0.19, 0.06], 0.3114		-0.11 [-0.20, -0.01], 0.0232	
heterogeneity (RR)						
p-value					0.4843	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4482	
Nervous system disorders						
n/N (%)	11/115 (9.6)	11/62 (17.7)	13/119 (10.9)	7/60 (11.7)	24/234 (10.3)	18/122 (14.8)
RR [95%-CI]; p-value	0.54 [0.25, 1.17], 0.1189		0.94 [0.39, 2.22], 0.8816		0.70 [0.39, 1.23], 0.2117	
OR [95%-CI]; p-value	0.49 [0.20, 1.21], 0.1157		0.93 [0.35, 2.46], 0.8817		0.66 [0.34, 1.27], 0.2118	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1423		-0.01 [-0.11, 0.09], 0.8828		-0.04 [-0.12, 0.03], 0.2334	
heterogeneity (RR)						
p-value					0.3519	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3446	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_2_m_soc_ae1pct_pp.sas using SAS 9.4

Table 12.4.4.1.2.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
n/N (%)	15/115 (13.0)	10/62 (16.1)	13/119 (10.9)	5/60 (8.3)	28/234 (12.0)	15/122 (12.3)
RR [95%-CI]; p-value	0.81 [0.39, 1.69], 0.5729		1.31 [0.49, 3.51], 0.5896		0.97 [0.54, 1.75], 0.9279	
OR [95%-CI]; p-value	0.78 [0.33, 1.86], 0.5739		1.35 [0.46, 3.98], 0.5864		0.97 [0.50, 1.89], 0.9279	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.5836		0.03 [-0.06, 0.12], 0.5710		-0.00 [-0.07, 0.07], 0.9282	
heterogeneity (RR)						
p-value					0.4414	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.4372	
Skin and subcutaneous tissue disorders						
n/N (%)	6/115 (5.2)	8/62 (12.9)	12/119 (10.1)	6/60 (10.0)	18/234 (7.7)	14/122 (11.5)
RR [95%-CI]; p-value	0.40 [0.15, 1.11], 0.0796		1.01 [0.40, 2.55], 0.9859		0.67 [0.35, 1.30], 0.2372	
OR [95%-CI]; p-value	0.37 [0.12, 1.12], 0.0707		1.01 [0.36, 2.84], 0.9859		0.64 [0.31, 1.34], 0.2362	
RD [95%-CI]; p-value	-0.08 [-0.17, 0.02], 0.1046		0.00 [-0.09, 0.09], 0.9859		-0.04 [-0.10, 0.03], 0.2617	
heterogeneity (RR)						
p-value					0.1925	
I^2					41.1%	
heterogeneity (OR)						
p-value					0.1923	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_2_m_soc_ae1pct_pp.sas using SAS 9.4

Table 12.4.4.1.2.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by SOC

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
n/N (%)	12/115 (10.4)	8/62 (12.9)	6/119 (5.0)	7/60 (11.7)	18/234 (7.7)	15/122 (12.3)
RR [95%-CI]; p-value	0.81 [0.35, 1.87], 0.6201		0.43 [0.15, 1.23], 0.1157		0.63 [0.33, 1.20], 0.1569	
OR [95%-CI]; p-value	0.79 [0.30, 2.04], 0.6207		0.40 [0.13, 1.25], 0.1069		0.59 [0.29, 1.23], 0.1552	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.08], 0.6300		-0.07 [-0.16, 0.02], 0.1502		-0.05 [-0.11, 0.02], 0.1816	
heterogeneity (RR)						
p-value					0.3597	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.3738	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s10_pp/T12_4_4_1_2_m_soc_ae1pct_pp.sas using SAS 9.4

Table 12.4.4.1.4.s10

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND≥ 1% in One Arm by PT

PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
n/N (%)	4/115 (3.5)	12/62 (19.4)	6/119 (5.0)	0/60 (0.0)	10/234 (4.3)	12/122 (9.8)
RR [95%-CI]; p-value	0.18 [0.06, 0.53], 0.0020		6.10 [0.35, 107.42], 0.2166		0.43 [0.19, 0.98], 0.0437	
OR [95%-CI]; p-value	0.15 [0.05, 0.49], 0.0004		6.37 [0.35, 116.02], 0.1530		0.41 [0.17, 0.98], 0.0386	
RD [95%-CI]; p-value	-0.16 [-0.26, -0.05], 0.0027		0.04 [-0.00, 0.09], 0.0691		-0.06 [-0.11, 0.00], 0.0640	
heterogeneity (RR)						
p-value					0.0243	
I^2					80.3%	
heterogeneity (OR)						
p-value					0.0028	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from lnRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.4.1.7.s10
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
n/N (%)	11/115 (9.6)	2/62 (3.2)	6/119 (5.0)	5/60 (8.3)	17/234 (7.3)	7/122 (5.7)
RR [95%-CI]; p-value	2.97 [0.68, 12.96], 0.1486		0.61 [0.19, 1.90], 0.3900		1.27 [0.54, 2.97], 0.5874	
OR [95%-CI]; p-value	3.17 [0.68, 14.80], 0.1230		0.58 [0.17, 2.00], 0.3867		1.29 [0.52, 3.19], 0.5854	
RD [95%-CI]; p-value	0.06 [-0.01, 0.13], 0.0736		-0.03 [-0.11, 0.05], 0.4214		0.02 [-0.04, 0.07], 0.5722	
heterogeneity (RR)						
p-value					0.0953	
I^2					64.1%	
heterogeneity (OR)						
p-value					0.0804	
Number of Patients with Any Severe SMQ of Acute Renal Failure						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)
RR [95%-CI]; p-value	1.09 [0.04, 31.95], 0.9614		NA		1.05 [0.04, 30.99], 0.9788	
OR [95%-CI]; p-value	1.09 [0.04, 32.88], 0.9614		NA		1.05 [0.03, 31.44], 0.9788	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9610		NA		0.00 [-0.01, 0.01], 0.9786	
heterogeneity (RR)						
p-value					0.7720	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.7706	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq_pp.sas using SAS 9.4

Table 12.4.4.1.7.s10
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
n/N (%)	10/115 (8.7)	2/62 (3.2)	6/119 (5.0)	5/60 (8.3)	16/234 (6.8)	7/122 (5.7)
RR [95%-CI]; p-value	2.70 [0.61, 11.92], 0.1910		0.61 [0.19, 1.90], 0.3900		1.19 [0.50, 2.82], 0.6897	
OR [95%-CI]; p-value	2.86 [0.61, 13.47], 0.1673		0.58 [0.17, 2.00], 0.3867		1.21 [0.48, 3.01], 0.6887	
RD [95%-CI]; p-value	0.05 [-0.01, 0.12], 0.1134		-0.03 [-0.11, 0.05], 0.4214		0.01 [-0.04, 0.06], 0.6809	
heterogeneity (RR)						
p-value					0.1187	
I^2					58.9%	
heterogeneity (OR)						
p-value					0.1043	
Number of Patients with Any Serious SMQ of Acute Renal Failure						
n/N (%)	5/115 (4.3)	1/62 (1.6)	1/119 (0.8)	0/60 (0.0)	6/234 (2.6)	1/122 (0.8)
RR [95%-CI]; p-value	2.70 [0.32, 22.56], 0.3603		1.02 [0.03, 29.88], 0.9923		3.13 [0.38, 25.69], 0.2884	
OR [95%-CI]; p-value	2.77 [0.32, 24.28], 0.3375		1.02 [0.03, 30.75], 0.9923		3.18 [0.38, 26.75], 0.2605	
RD [95%-CI]; p-value	0.03 [-0.02, 0.08], 0.2711		0.00 [-0.03, 0.03], 0.9923		0.02 [-0.01, 0.04], 0.1853	
heterogeneity (RR)						
p-value					0.6322	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.6185	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq_pp.sas using SAS 9.4

Table 12.4.4.1.7.s10
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
n/N (%)	10/115 (8.7)	9/62 (14.5)	9/119 (7.6)	5/60 (8.3)	19/234 (8.1)	14/122 (11.5)
RR [95%-CI]; p-value	0.60 [0.26, 1.40], 0.2351		0.91 [0.32, 2.59], 0.8561		0.71 [0.37, 1.36], 0.3004	
OR [95%-CI]; p-value	0.56 [0.21, 1.46], 0.2327		0.90 [0.29, 2.81], 0.8562		0.68 [0.33, 1.41], 0.3001	
RD [95%-CI]; p-value	-0.06 [-0.16, 0.04], 0.2619		-0.01 [-0.09, 0.08], 0.8583		-0.03 [-0.10, 0.03], 0.3227	
heterogeneity (RR)						
p-value					0.5455	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5330	
Number of Patients with Any Severe SMQ of Cardiac Failure						
n/N (%)	1/115 (0.9)	0/62 (0.0)	2/119 (1.7)	1/60 (1.7)	3/234 (1.3)	1/122 (0.8)
RR [95%-CI]; p-value	1.09 [0.04, 31.95], 0.9614		1.01 [0.09, 10.90], 0.9945		1.56 [0.16, 14.88], 0.6971	
OR [95%-CI]; p-value	1.09 [0.04, 32.88], 0.9614		1.01 [0.09, 11.35], 0.9945		1.57 [0.16, 15.27], 0.6944	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9610		0.00 [-0.04, 0.04], 0.9945		0.00 [-0.02, 0.03], 0.6739	
heterogeneity (RR)						
p-value					0.9716	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.9717	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq_pp.sas using SAS 9.4

Table 12.4.4.1.7.s10
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
n/N (%)	9/115 (7.8)	9/62 (14.5)	8/119 (6.7)	5/60 (8.3)	17/234 (7.3)	14/122 (11.5)
RR [95%-CI]; p-value	0.54 [0.23, 1.29], 0.1644		0.81 [0.28, 2.36], 0.6949		0.63 [0.32, 1.24], 0.1829	
OR [95%-CI]; p-value	0.50 [0.19, 1.33], 0.1601		0.79 [0.25, 2.54], 0.6951		0.60 [0.29, 1.27], 0.1811	
RD [95%-CI]; p-value	-0.07 [-0.17, 0.03], 0.1919		-0.02 [-0.10, 0.07], 0.7042		-0.04 [-0.11, 0.02], 0.2085	
heterogeneity (RR)						
p-value					0.5677	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5519	
Number of Patients with Any Serious SMQ of Cardiac Failure						
n/N (%)	4/115 (3.5)	0/62 (0.0)	3/119 (2.5)	1/60 (1.7)	7/234 (3.0)	1/122 (0.8)
RR [95%-CI]; p-value	4.35 [0.23, 80.92], 0.3245		1.51 [0.16, 14.23], 0.7175		3.65 [0.45, 29.32], 0.2234	
OR [95%-CI]; p-value	4.47 [0.23, 85.92], 0.2783		1.53 [0.16, 14.99], 0.7151		3.73 [0.45, 30.68], 0.1895	
RD [95%-CI]; p-value	0.03 [-0.01, 0.07], 0.1907		0.01 [-0.03, 0.05], 0.6965		0.02 [-0.01, 0.05], 0.1157	
heterogeneity (RR)						
p-value					0.5743	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.5633	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure, Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea, Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_7_m_pt_smq_pp.sas using SAS 9.4

Table 12.4.4.1.6.s10
Overall Summary of Adverse Drug Reactions (ADR)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
n/N (%)	16/115 (13.9)	17/62 (27.4)	23/119 (19.3)	7/60 (11.7)	39/234 (16.7)	24/122 (19.7)
RR [95%-CI]; p-value	0.51 [0.28, 0.93], 0.0290		1.66 [0.75, 3.64], 0.2087		0.85 [0.54, 1.34], 0.4790	
OR [95%-CI]; p-value	0.43 [0.20, 0.92], 0.0277		1.81 [0.73, 4.51], 0.1952		0.82 [0.46, 1.43], 0.4807	
RD [95%-CI]; p-value	-0.14 [-0.26, -0.01], 0.0383		0.08 [-0.03, 0.18], 0.1638		-0.03 [-0.12, 0.06], 0.4892	
heterogeneity (RR)						
p-value					0.0198	
I^2					81.6%	
heterogeneity (OR)						
p-value					0.0157	
Number of Patients with Any Severe ADR						
n/N (%)	0/115 (0.0)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	0/122 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
heterogeneity (RR)						
p-value					NA	
I^2					NA	
heterogeneity (OR)						
p-value					NA	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_6_m_pt_adr_pp.sas using SAS 9.4

Table 12.4.4.1.6.s10
Overall Summary of Adverse Drug Reactions (ADR)
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious ADR						
n/N (%)	0/115 (0.0)	0/62 (0.0)	1/119 (0.8)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)
RR [95%-CI]; p-value	0.54 [0.01, 26.94], 0.7581		1.02 [0.03, 29.88], 0.9923		1.05 [0.04, 30.99], 0.9788	
OR [95%-CI]; p-value	0.54 [0.01, 27.50], 0.7544		1.02 [0.03, 30.75], 0.9923		1.05 [0.03, 31.44], 0.9788	
RD [95%-CI]; p-value	-0.00 [-0.03, 0.02], 0.7746		0.00 [-0.03, 0.03], 0.9923		0.00 [-0.01, 0.01], 0.9786	
heterogeneity (RR)						
p-value					0.8109	
I^2					0.0%	
heterogeneity (OR)						
p-value					0.8102	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/b3/T12_4_4_1_6_m_pt_adr_pp.sas using SAS 9.4

Table 12.4.9.1.1.s10
Summary of TEAE Leading to Study Discontinuation by SOC
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with AE leading to death						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)
Number of Patients with AE leading to treatment discontinuation						
n/N (%)	8/115 (7.0)	3/62 (4.8)	5/119 (4.2)	0/60 (0.0)	13/234 (5.6)	3/122 (2.5)
Number of Patients with AE leading to study discontinuation						
n/N (%)	1/115 (0.9)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	1/122 (0.8)
Infections and infestations						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)
Investigations						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)
Metabolism and nutrition disorders						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)

Abbreviations: ER: Extended Release; PP: Per-Protocol; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.1.s10
Summary of TEAE Leading to Study Discontinuation by SOC
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)
Psychiatric disorders						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)

Abbreviations: ER: Extended Release; PP: Per-Protocol; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2.s10
Summary of TEAE Leading to Study Discontinuation by PT
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with AE leading to death						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)
Number of Patients with AE leading to treatment discontinuation						
n/N (%)	8/115 (7.0)	3/62 (4.8)	5/119 (4.2)	0/60 (0.0)	13/234 (5.6)	3/122 (2.5)
Number of Patients with AE leading to study discontinuation						
n/N (%)	1/115 (0.9)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	1/122 (0.8)
Infections and infestations						
Pneumonia						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)
Investigations						
Blood creatinine increased						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)

Abbreviations: ER: Extended Release; PP: Per-Protocol; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.9.1.2.s10
Summary of TEAE Leading to Study Discontinuation by PT
PP Population

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Fluid overload						
n/N (%)	1/115 (0.9)	0/62 (0.0)	0/119 (0.0)	0/60 (0.0)	1/234 (0.4)	0/122 (0.0)
Musculoskeletal and connective tissue disorders						
Muscular weakness						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)
Psychiatric disorders						
Hallucination						
n/N (%)	0/115 (0.0)	1/62 (1.6)	0/119 (0.0)	0/60 (0.0)	0/234 (0.0)	1/122 (0.8)

Abbreviations: ER: Extended Release; PP: Per-Protocol; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Table 12.4.8.1.2.s10

Summary of SAE Occurring ≥ 5% in One Arm by PT

PP Population

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The heterogeneity p-value (RR) and I^2 are calculated from InRR using the fixed-effect model. The heterogeneity p-value (OR) is based on the Breslow-Day test for homogeneity of the odds ratios between studies. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment. N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

Nachberechnungsdokument
Forest Plots - Wirksamkeitsendpunkte (ITT-Population)

Folgende Daten werden für die ITT-Population dargestellt:

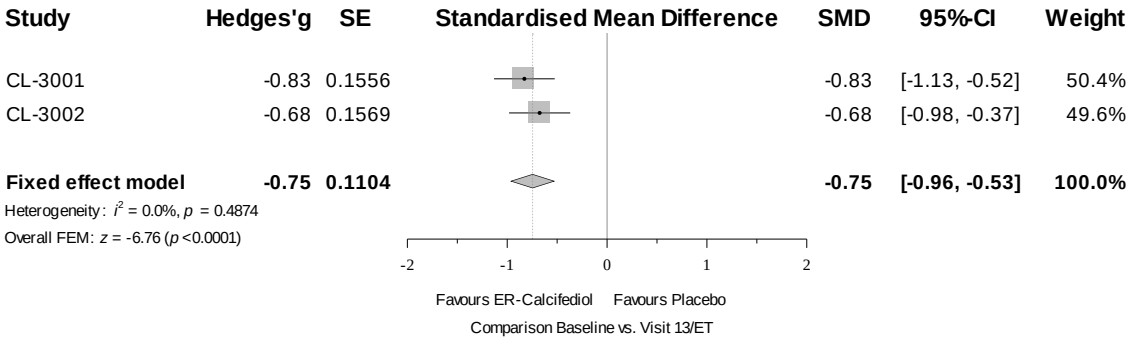
iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einem 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

Figure 12.2.2.1 Mean Change from Baseline in Plasma iPTH (pg/mL)
ITT Population



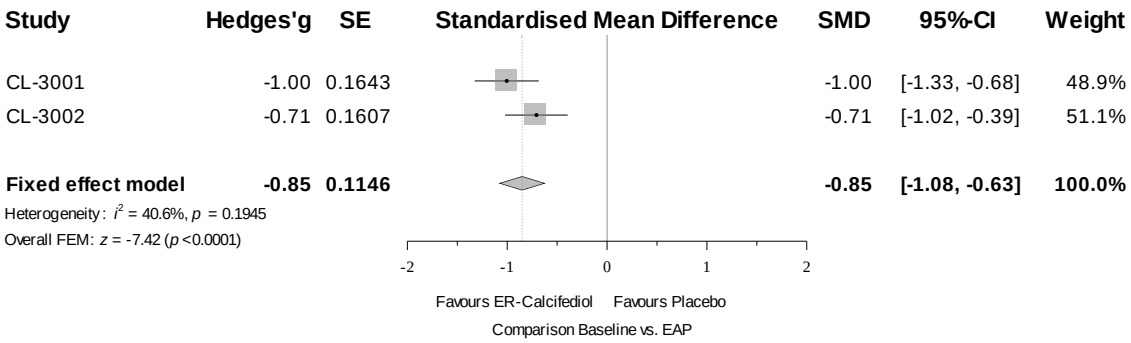
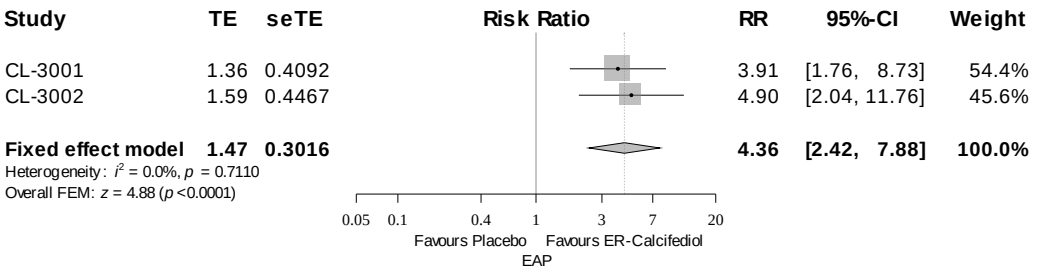


Figure 12.2.1.1.1 Number of Patients with iPTH Reduction ≥ 30%
ITT Population



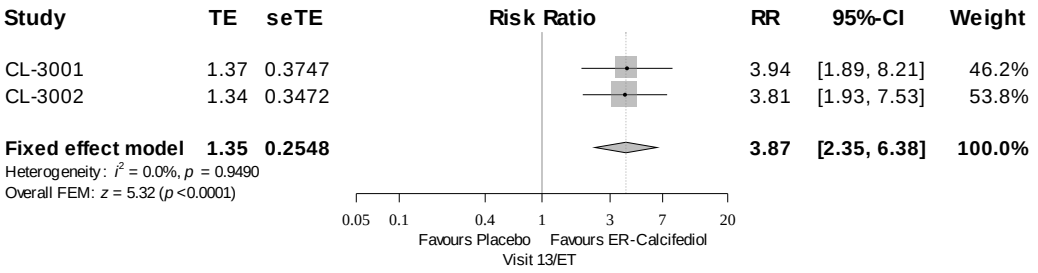
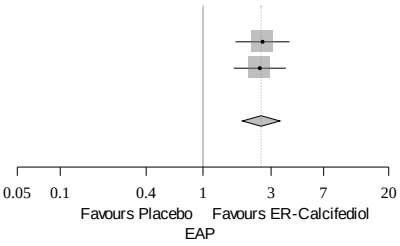


Figure 12.2.1.1.2 Number of Patients with iPTH Reduction ≥ 10%
ITT Population

Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.96	0.2221	2.61	[1.69, 4.04]	48.2%
CL-3002	0.92	0.2141	2.50	[1.64, 3.80]	51.8%
Fixed effect model	**0.94**	**0.1542**	**2.56**	**[1.89, 3.46]**	**100.0%**

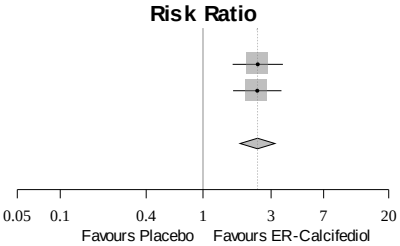
Heterogeneity: $I^2 = 0.0\%$, $p = 0.8858$
Overall FEM: $z = 6.09$ ($p < 0.0001$)



EAP

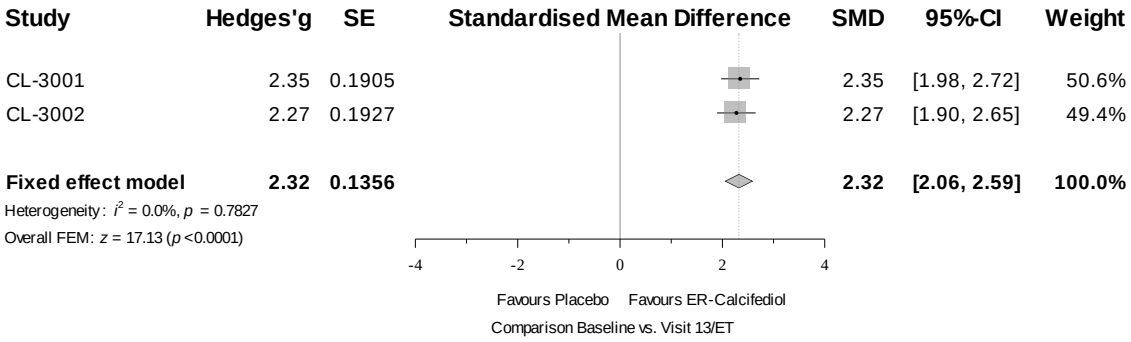
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.88	0.2068	2.42	[1.61, 3.63]	48.1%
CL-3002	0.88	0.1990	2.40	[1.63, 3.54]	51.9%
Fixed effect model	**0.88**	**0.1434**	**2.41**	**[1.82, 3.19]**	**100.0%**

Heterogeneity: $I^2 = 0.0\%$, $p = 0.9783$
Overall FEM: $z = 6.13$ ($p < 0.0001$)



Visit 13/ET

Figure 12.3.2.1 Mean Change from Baseline in Serum Total 25-Hydroxyvitamin D (ng/mL)
ITT Population



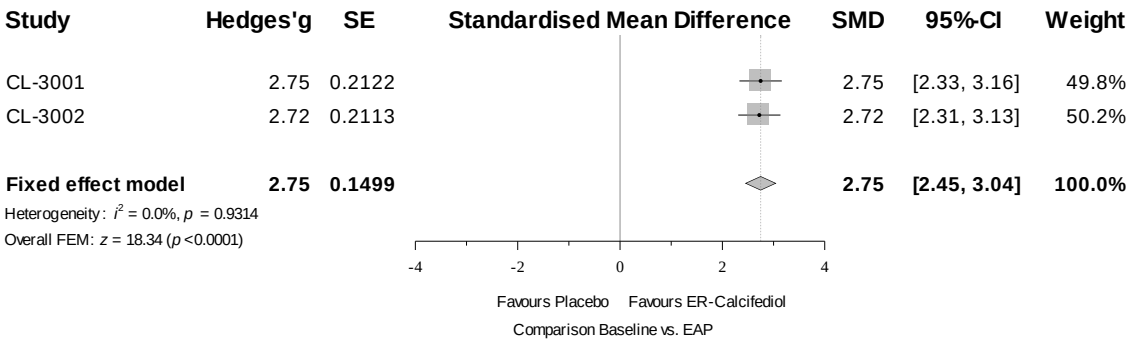
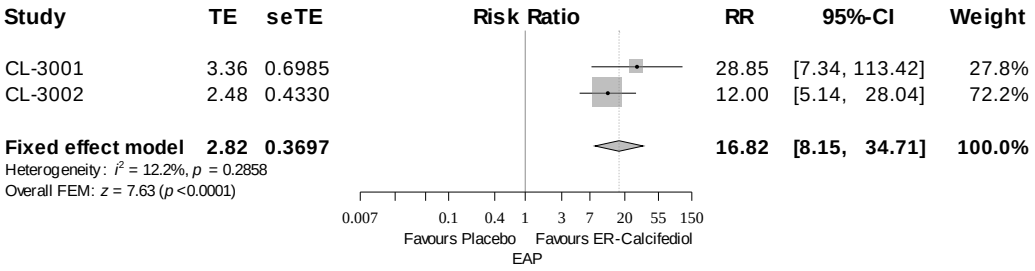
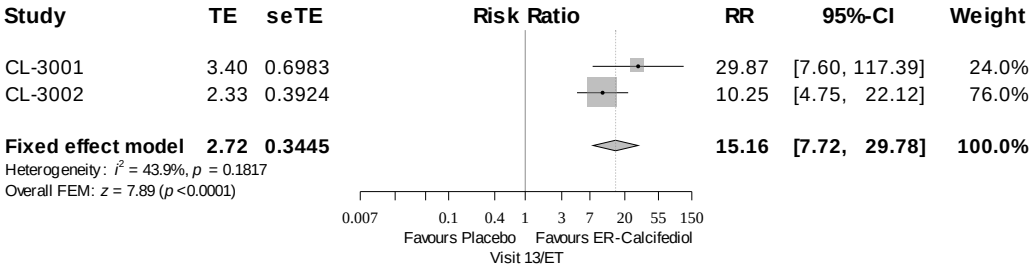


Figure 12.3.1.1 Number of Patients with Adequate Serum 25 D Levels (≥30 ng/mL) ITT Population





Nachberechnungsdokument
Forest Plots - Wirksamkeitsendpunkte (PP-Population)

Folgende Daten werden für die PP-Population dargestellt:

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

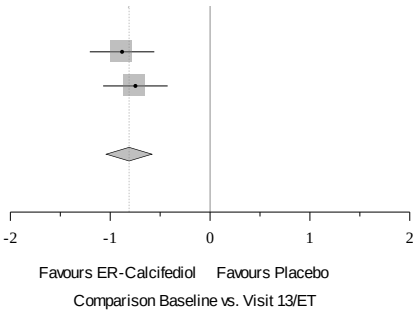
25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einem 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

Figure 12.2.2.1.s10 Mean Change from Baseline in Plasma iPTH (pg/mL) PP Population

Study	Hedges'g	SE	Standardised Mean Difference	SMD	95%-CI	Weight
CL-3001	-0.88	0.1655		-0.88	[-1.20, -0.56]	50.0%
CL-3002	-0.75	0.1655		-0.75	[-1.07, -0.42]	50.0%
Fixed effect model	**-0.81**	**0.1169**		**-0.81**	**[-1.04, -0.58]**	**100.0%**

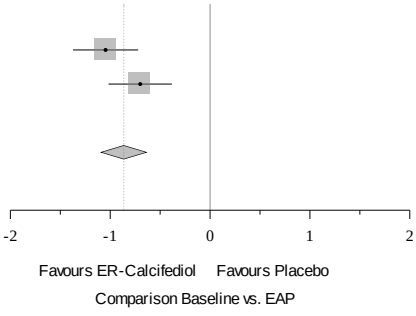
Heterogeneity: i^2 = 0.0%, p = 0.5665
Overall FEM: z = -6.93 (p <0.0001)



Comparison Baseline vs. Visit 13/ET

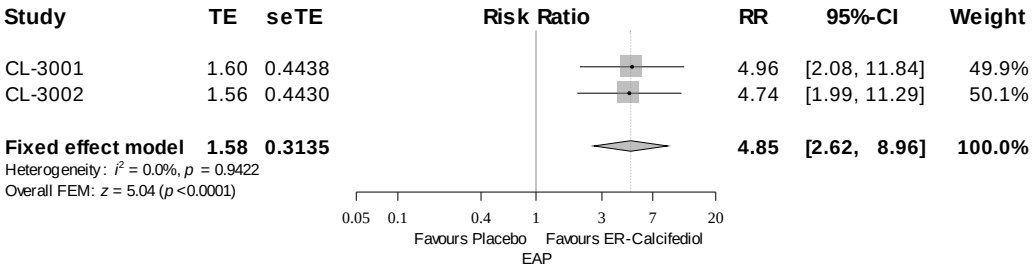
Study	Hedges'g	SE	Standardised Mean Difference	SMD	95%-CI	Weight
CL-3001	-1.05	0.1672		-1.05	[-1.37, -0.72]	48.6%
CL-3002	-0.70	0.1626		-0.70	[-1.02, -0.38]	51.4%
Fixed effect model	**-0.86**	**0.1163**		**-0.86**	**[-1.09, -0.64]**	**100.0%**

Heterogeneity: i^2 = 55.2%, p = 0.1352
Overall FEM: z = -7.43 (p <0.0001)



Comparison Baseline vs. EAP

Figure 12.2.1.1.1.s10 Number of Patients with iPTH Reduction ≥ 30%
PP Population



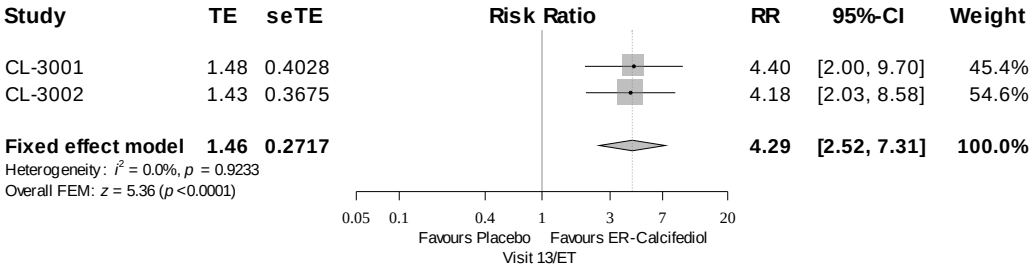
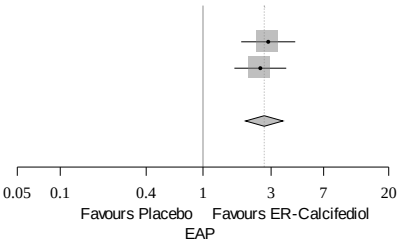


Figure 12.2.1.1.2.s10 Number of Patients with iPTH Reduction ≥ 10%
PP Population

Study	TE	seTE	RR	95%-CI	Weight
CL-3001	1.05	0.2224	2.86	[1.85, 4.43]	47.9%
CL-3002	0.92	0.2133	2.52	[1.66, 3.83]	52.1%
Fixed effect model	**0.99**	**0.1540**	**2.69**	**[1.99, 3.63]**	**100.0%**

Heterogeneity: $I^2 = 0.0\%$, $p = 0.6788$
Overall FEM: $z = 6.42$ ($p < 0.0001$)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	1.03	0.2338	2.80	[1.77, 4.43]	43.4%
CL-3002	0.89	0.2049	2.44	[1.63, 3.64]	56.6%
Fixed effect model	**0.96**	**0.1546**	**2.61**	**[1.93, 3.53]**	**100.0%**

Heterogeneity: $I^2 = 0.0\%$, $p = 0.6522$
Overall FEM: $z = 6.20$ ($p < 0.0001$)

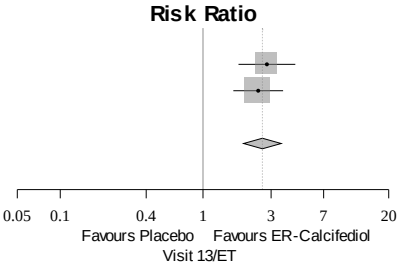
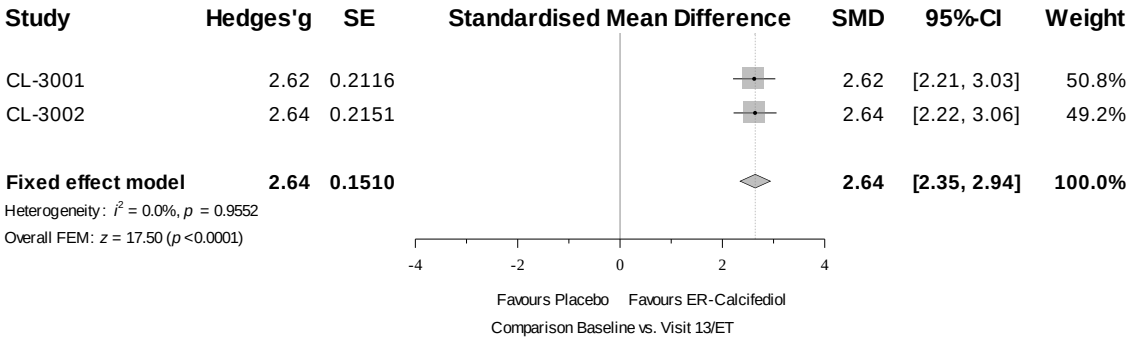


Figure 12.3.2.1.s10 Mean Change from Baseline in Serum Total 25-Hydroxyvitamin D (ng/mL) PP Population



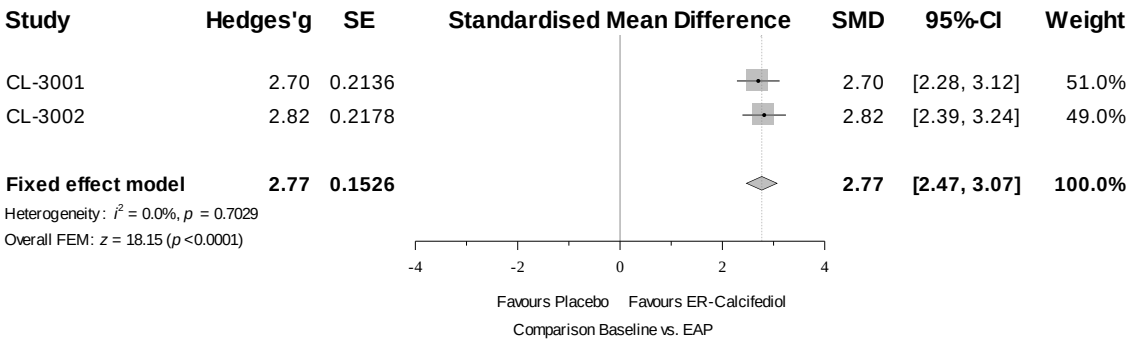
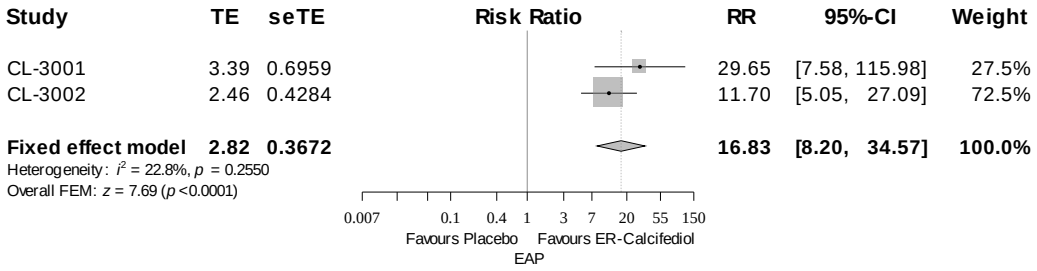
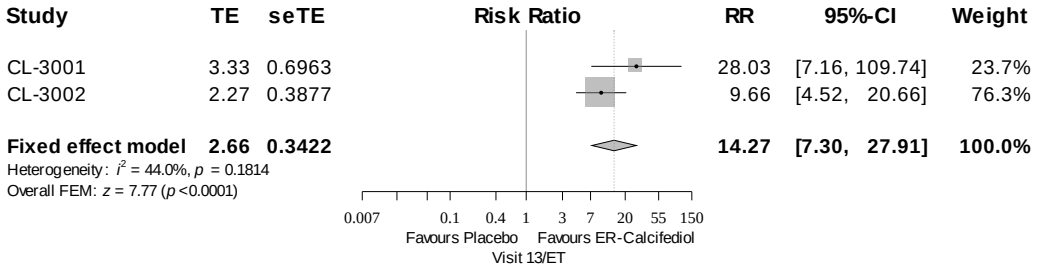


Figure 12.3.1.1.s10 Number of Patients with Adequate Serum 25 D Levels (≥30 ng/mL)
PP Population





Nachberechnungsdokument
Forest Plots - Sicherheitsendpunkte
Sicherheits-relevante sHPT-assoziierte Parameter (ITT-Population)

Folgende Daten werden für die ITT-Population dargestellt:

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperkalzämie
- Anteil Patienten mit einer Hyperkalzurie

- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperphosphatämie

- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum

- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

Figure 12.4.12.1.1 Mean Change from Baseline in Serum Calcium (mg/dL)
ITT Population

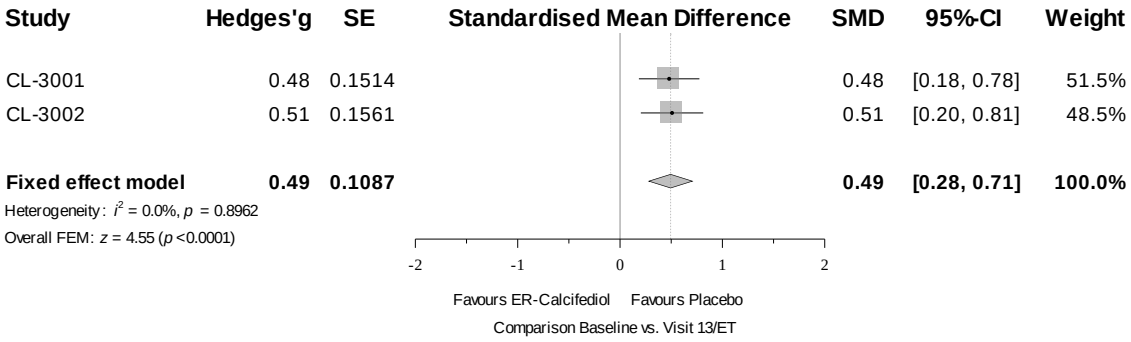


Figure 12.4.19.1.2 Number of Patients with Hypercalcemia (two consecutive visits with serum Ca >10.3 mg/dL) ITT Population

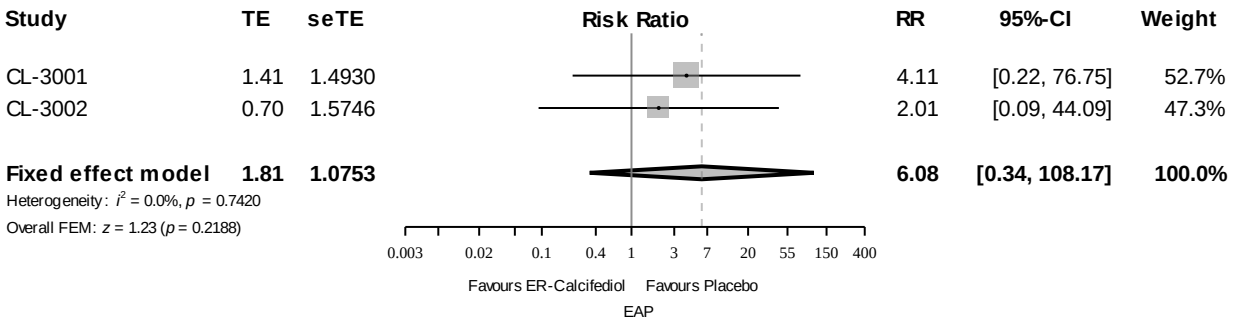


Figure 12.4.15.1.3 Number of Patients with Hypercalciuria (>200 mg calcium/g creatinine)
ITT Population

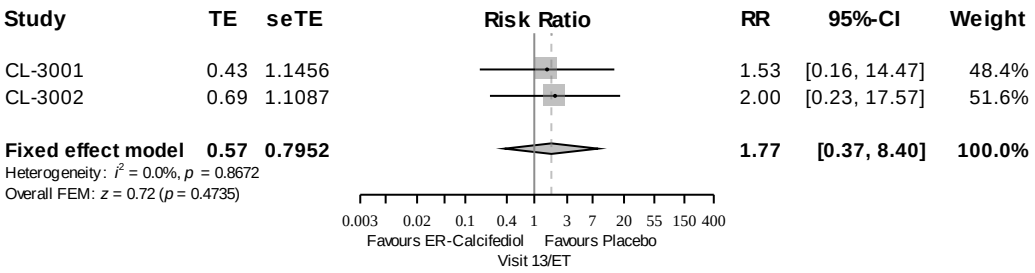
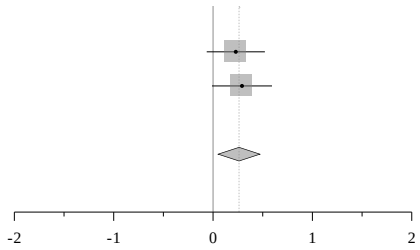


Figure 12.4.14.1 Mean Change from Baseline in Serum Phosphorus (mg/dL) ITT Population

Study	Hedges'g	SE	SMD	95%-CI	Weight
CL-3001	0.23	0.1499	0.23	[-0.06, 0.52]	51.6%
CL-3002	0.29	0.1547	0.29	[-0.01, 0.59]	48.4%
Fixed effect model	**0.26**	**0.1076**	**0.26**	**[0.05, 0.47]**	**100.0%**

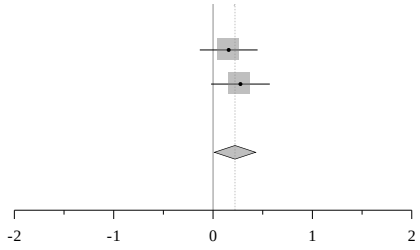
Heterogeneity: i^2 = 0.0%, p = 0.7711
Overall FEM: z = 2.43 (p = 0.0151)



Comparison Baseline vs. Visit 13/ET

Study	Hedges'g	SE	SMD	95%-CI	Weight
CL-3001	0.16	0.1490	0.16	[-0.13, 0.45]	50.8%
CL-3002	0.28	0.1514	0.28	[-0.02, 0.57]	49.2%
Fixed effect model	**0.22**	**0.1062**	**0.22**	**[0.01, 0.43]**	**100.0%**

Heterogeneity: i^2 = 0.0%, p = 0.5767
Overall FEM: z = 2.08 (p = 0.0375)



Comparison Baseline vs. EAP

Figure 12.4.19.1.1 Number of Patients with Hyperphosphatemia (two consecutive visits with serum P >5.5 mg/dL) ITT Population

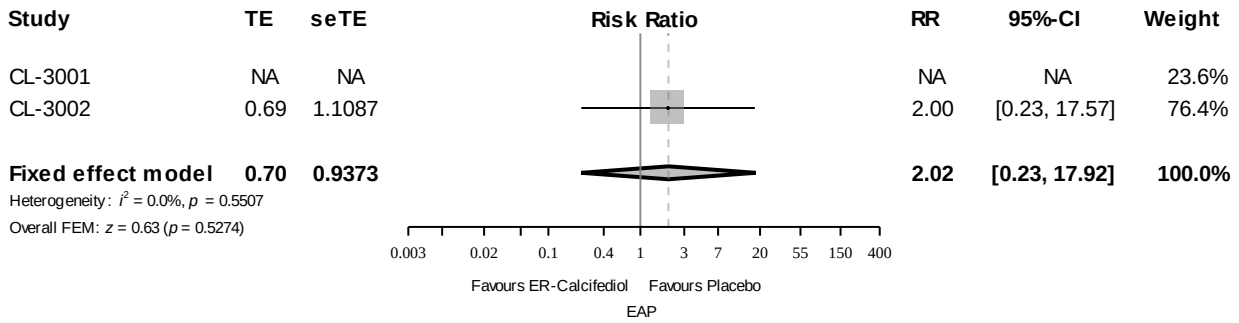
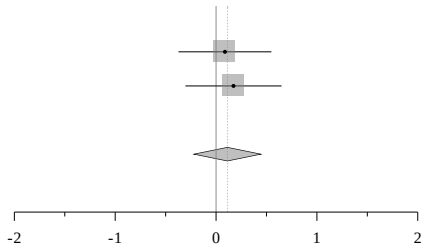


Figure 12.5.1.1.1 Mean Change from Baseline in Serum FGF-23 (pg/mL) ITT Population

Study	Hedges'g	SE	SMD	95%-CI	Weight
CL-3001	0.09	0.2371	0.09	[-0.37, 0.55]	51.7%
CL-3002	0.17	0.2457	0.17	[-0.30, 0.65]	48.3%
Fixed effect model	**0.11**	**0.1703**	**0.11**	**[-0.22, 0.44]**	**100.0%**

Heterogeneity: i^2 = 0.0%, p = 0.8015

Overall FEM: z = 0.66 (p = 0.5091)



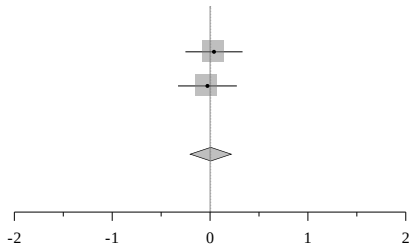
Comparison Baseline vs. Visit 13/ET

Figure 12.4.12.1.2 Mean Change from Baseline in eGFR (mL/min/1.73m2)
ITT Population

Study	Hedges'g	SE	SMD	95%-CI	Weight
CL-3001	0.04	0.1495	0.04	[-0.25, 0.33]	51.5%
CL-3002	-0.03	0.1540	-0.03	[-0.33, 0.27]	48.5%
Fixed effect model	**0.01**	**0.1072**	**0.01**	**[-0.20, 0.22]**	**100.0%**

Heterogeneity: i^2 = 0.0%, p = 0.7543

Overall FEM: z = 0.07 (p = 0.9459)



Comparison Baseline vs. Visit 13/ET

Nachberechnungsdokument
Forest Plots - Sicherheitsendpunkte
Sicherheits-relevante sHPT-assoziierte Parameter (PP-Population)

Folgende Daten werden für die PP-Population dargestellt:

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperkalzämie
- Anteil Patienten mit einer Hyperkalzurie

- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Anteil Patienten mit einer Hyperphosphatämie

- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum

- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

Figure 12.4.12.1.1.s10 Mean Change from Baseline in Serum Calcium (mg/dL) PP Population

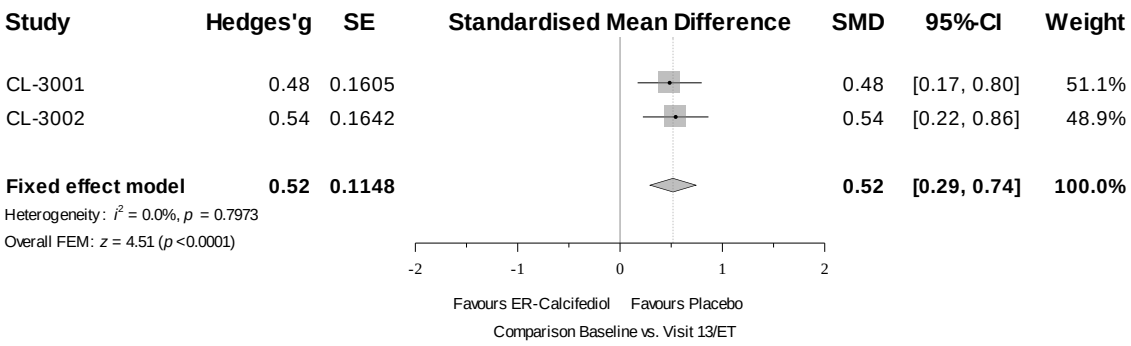


Figure 12.4.19.1.2.s10 Number of Patients with Hypercalcemia (two consecutive visits with serum Ca >10.3 mg/dL) PP Population

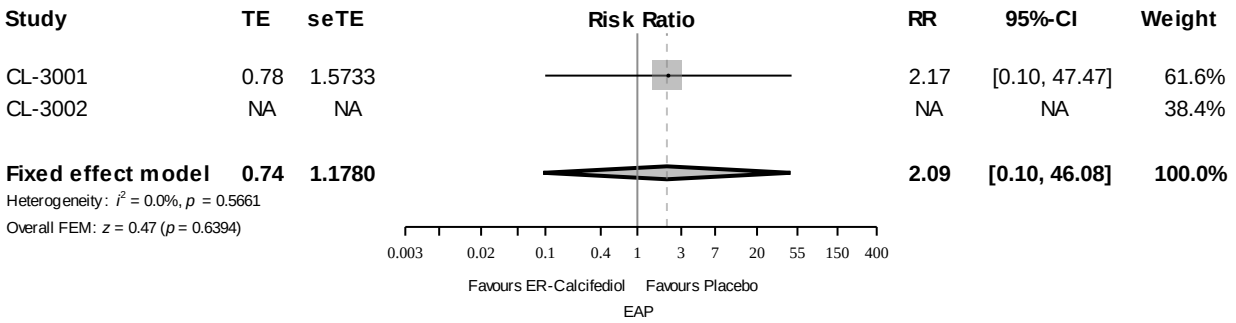


Figure 12.4.15.1.3.s10 Number of Patients with Hypercalciuria (>200 mg calcium/g creatinine)
PP Population

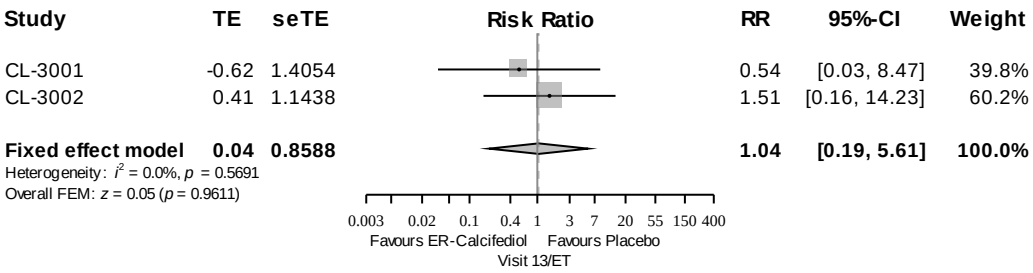
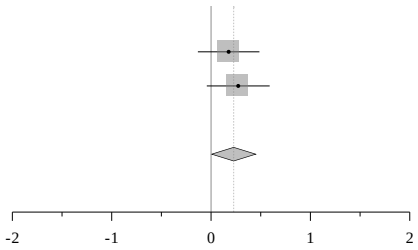


Figure 12.4.14.1.s10 Mean Change from Baseline in Serum Phosphorus (mg/dL) PP Population

Study	Hedges'g	SE	SMD	95%-CI	Weight
CL-3001	0.18	0.1587	0.18	[-0.13, 0.49]	51.1%
CL-3002	0.27	0.1622	0.27	[-0.04, 0.59]	48.9%
Fixed effect model	**0.23**	**0.1134**	**0.23**	**[0.01, 0.45]**	**100.0%**

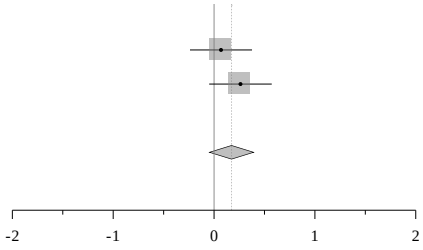
Heterogeneity: i^2 = 0.0%, p = 0.6697
Overall FEM: z = 2.01 (p = 0.0445)



Comparison Baseline vs. Visit 13/ET

Study	Hedges'g	SE	SMD	95%-CI	Weight
CL-3001	0.07	0.1576	0.07	[-0.24, 0.38]	50.4%
CL-3002	0.26	0.1589	0.26	[-0.05, 0.57]	49.6%
Fixed effect model	**0.17**	**0.1119**	**0.17**	**[-0.05, 0.39]**	**100.0%**

Heterogeneity: i^2 = 0.0%, p = 0.3862
Overall FEM: z = 1.55 (p = 0.1212)



Comparison Baseline vs. EAP

Figure 12.4.19.1.1.s10 Number of Patients with Hyperphosphatemia (two consecutive visits with serum P >5.5 mg/dL) PP Population

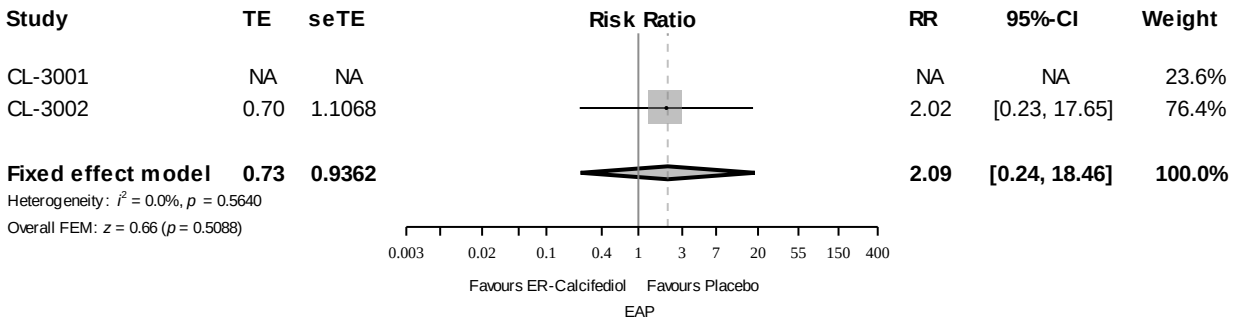


Figure 12.5.1.1.1.s10 Mean Change from Baseline in Serum FGF-23 (pg/mL) PP Population

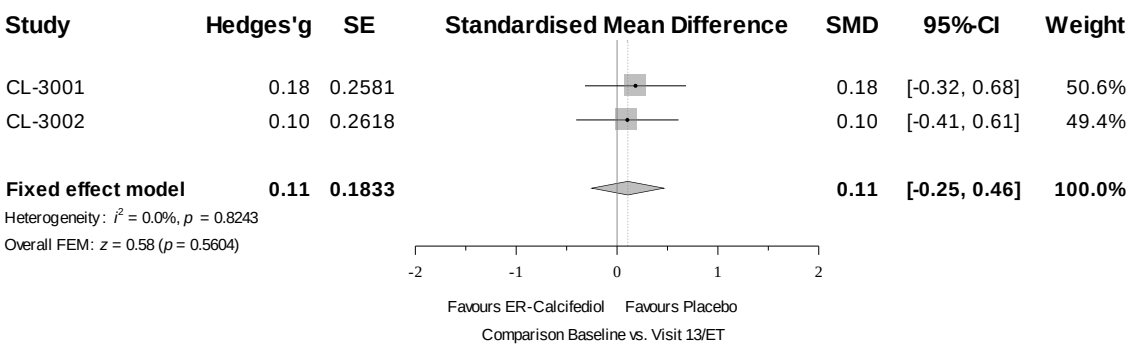


Figure 12.4.12.1.2.s10 Mean Change from Baseline in eGFR (mL/min/1.73m2) PP Population

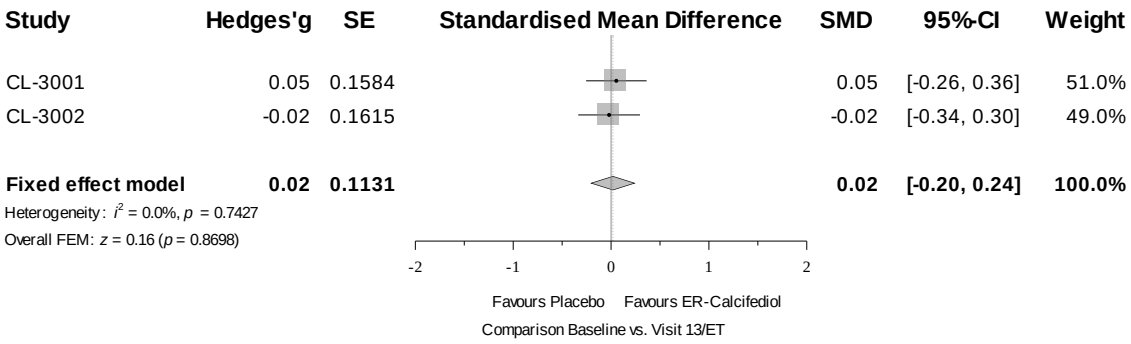
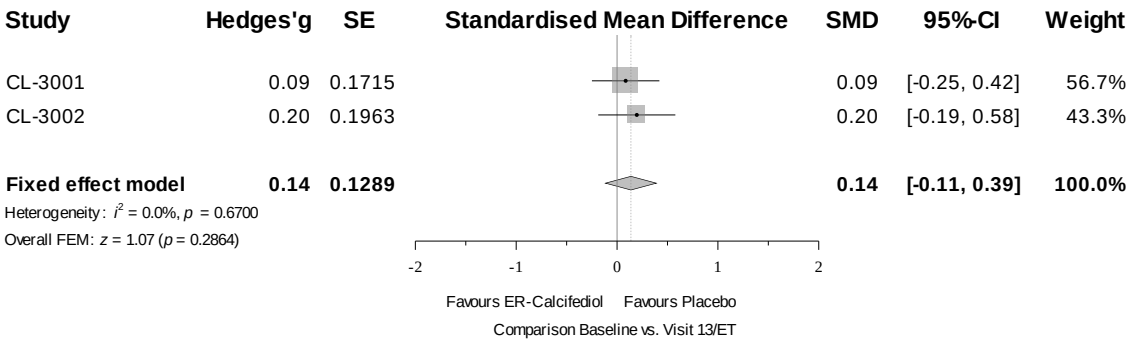


Figure 12.4.15.1.1.s10 Mean Change from Baseline in Urine Albumin/Creatinine (g/g Creatinine)
PP Population

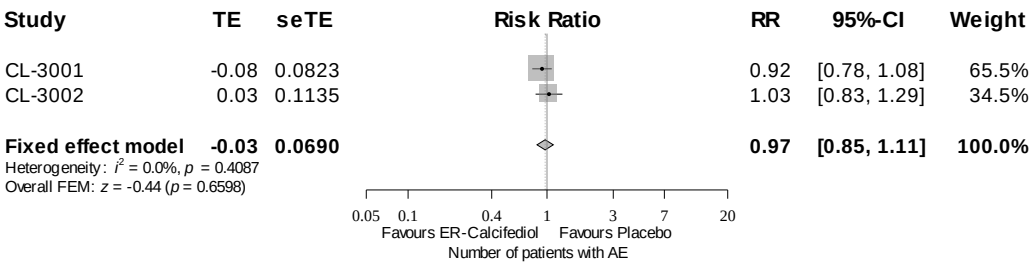


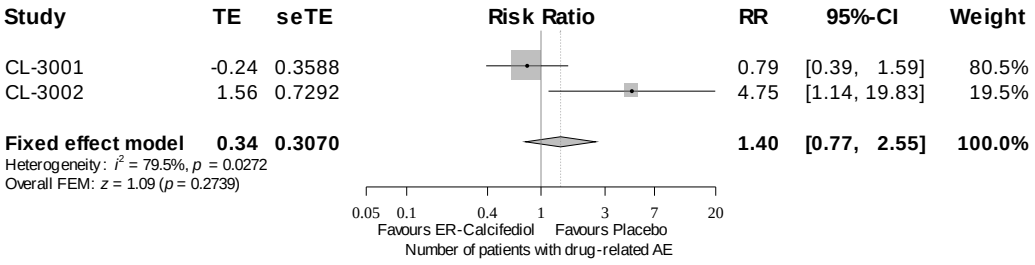
Nachberechnungsdokument
Forest Plots - Sicherheitsendpunkte
Unerwünschte Ereignisse
(ITT-Population)

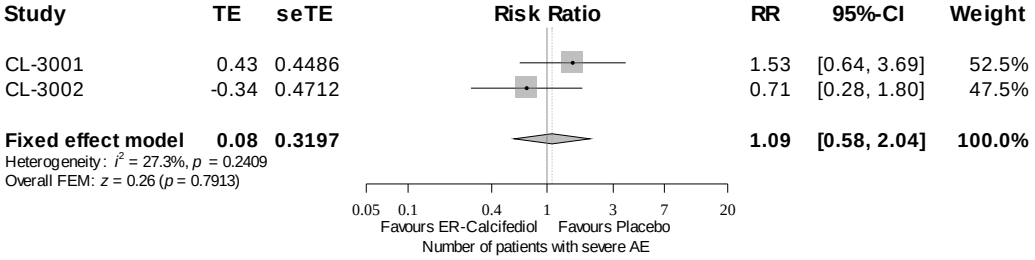
Folgende Daten werden für die ITT-Population dargestellt:

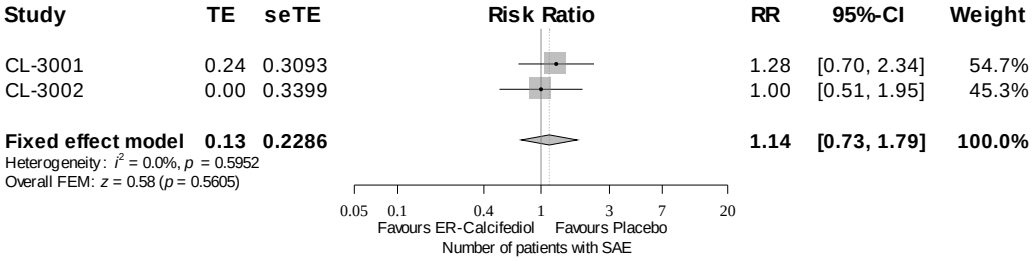
- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (SMQs)
  - UE ohne erkrankungsbezogene Ereignisse

Figure 12.4.3.1 Summary of TEAE
ITT Population









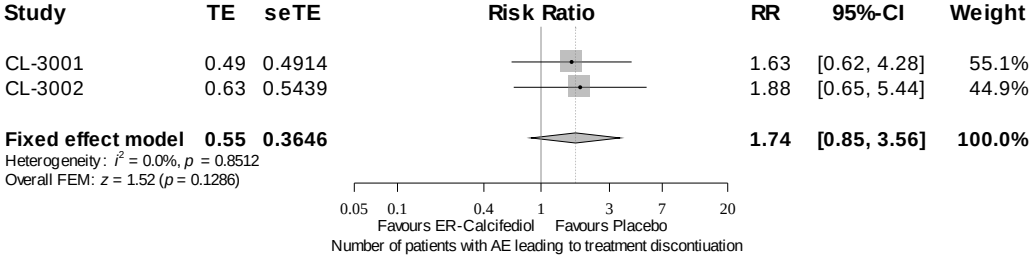
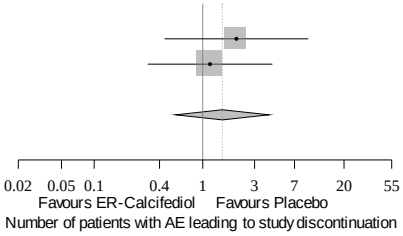


Figure 12.4.3.1 Summary of TEAE
ITT Population

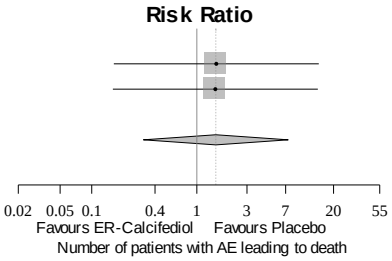
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.71	0.7772	2.04	[0.45, 9.37]	43.0%
CL-3002	0.15	0.6748	1.17	[0.31, 4.38]	57.0%
Fixed effect model	**0.42**	**0.5062**	**1.52**	**[0.56, 4.09]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.5864
Overall FEM: z = 0.82 (p = 0.4112)



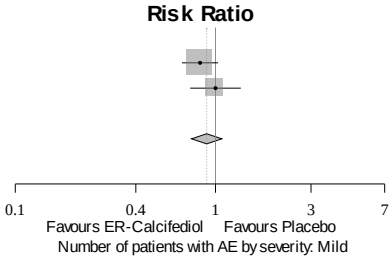
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.43	1.1456	1.53	[0.16, 14.47]	50.0%
CL-3002	0.41	1.1456	1.50	[0.16, 14.17]	50.0%
Fixed effect model	**0.42**	**0.8101**	**1.52**	**[0.31, 7.42]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.9896
Overall FEM: z = 0.51 (p = 0.6076)



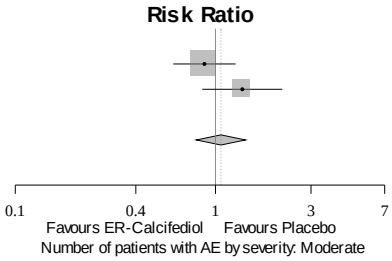
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.18	0.1059	0.84	[0.68, 1.03]	66.3%
CL-3002	0.00	0.1484	1.00	[0.75, 1.34]	33.7%
Fixed effect model	**-0.10**	**0.0888**	**0.90**	**[0.76, 1.08]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.3305
Overall FEM: z = -1.14 (p = 0.2534)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.13	0.1830	0.88	[0.62, 1.26]	62.2%
CL-3002	0.31	0.2348	1.36	[0.86, 2.16]	37.8%
Fixed effect model	**0.06**	**0.1447**	**1.06**	**[0.80, 1.41]**	**100.0%**

Heterogeneity: I^2 = 53.3%, p = 0.1434
Overall FEM: z = 0.43 (p = 0.6667)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.43	0.4486	1.53	[0.64, 3.69]	52.5%
CL-3002	-0.34	0.4712	0.71	[0.28, 1.80]	47.5%
Fixed effect model	**0.08**	**0.3197**	**1.09**	**[0.58, 2.04]**	**100.0%**

Heterogeneity: I^2 = 27.3%, p = 0.2409
Overall FEM: z = 0.26 (p = 0.7913)

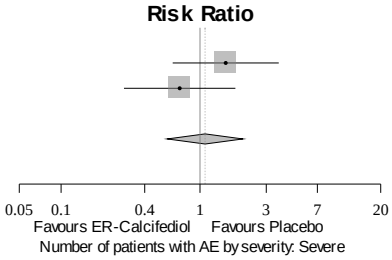
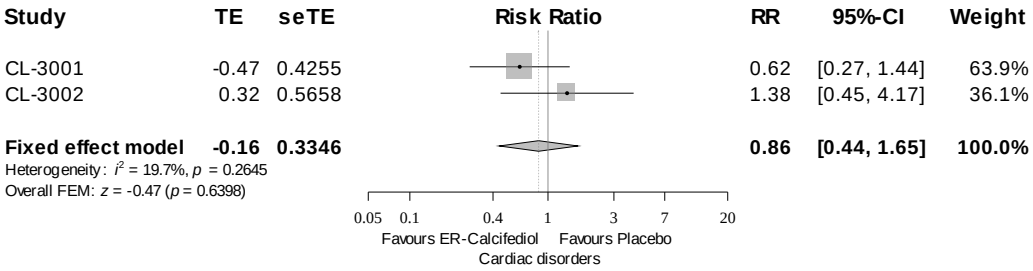
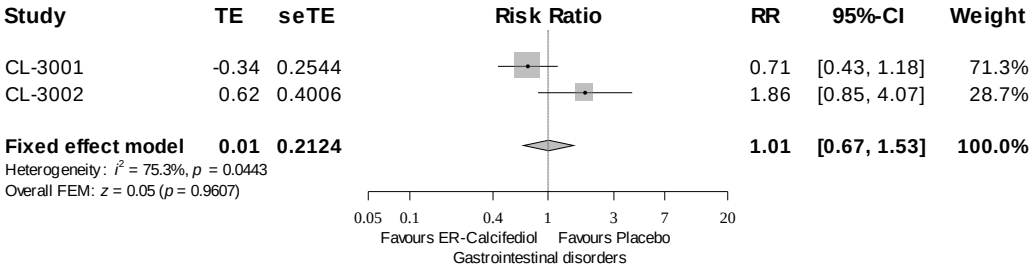
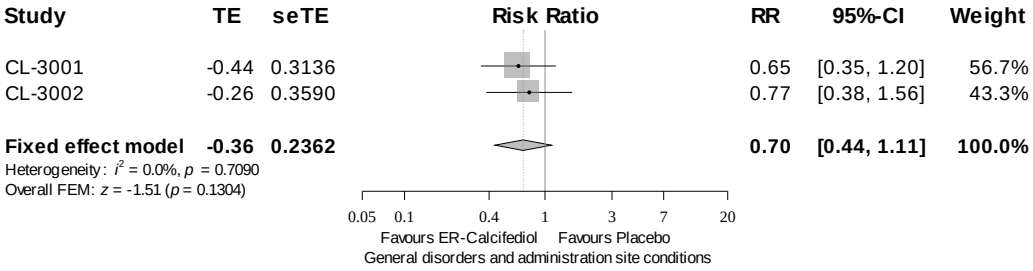
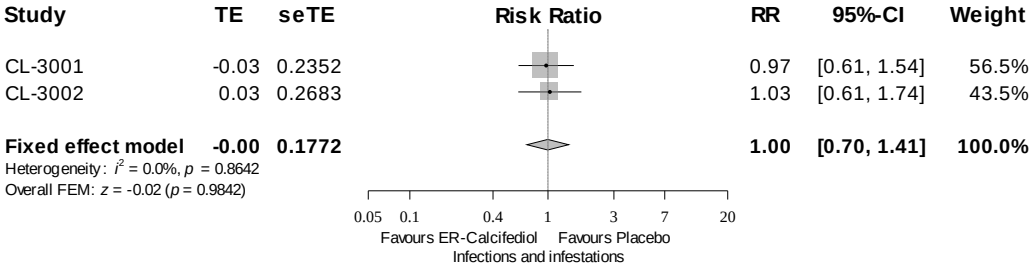


Figure 12.4.4.1.1 TEAE (independent of severity) Occurring ≥ 10% in One Arm by SOC
ITT Population









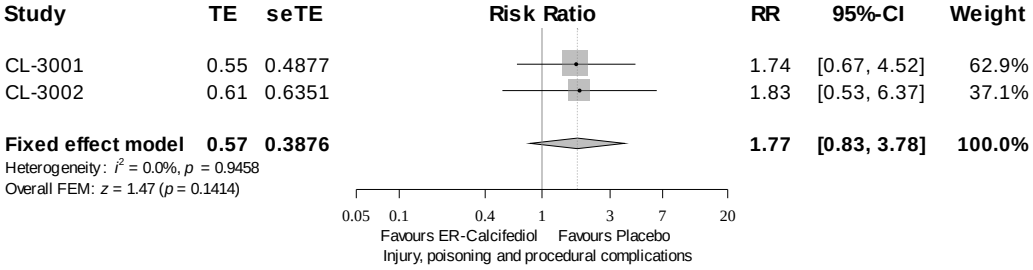
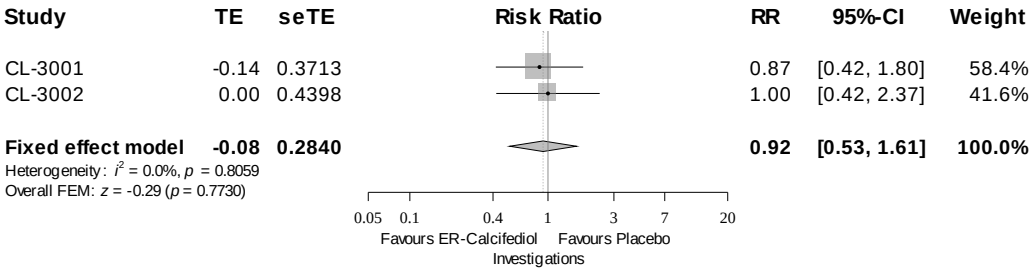
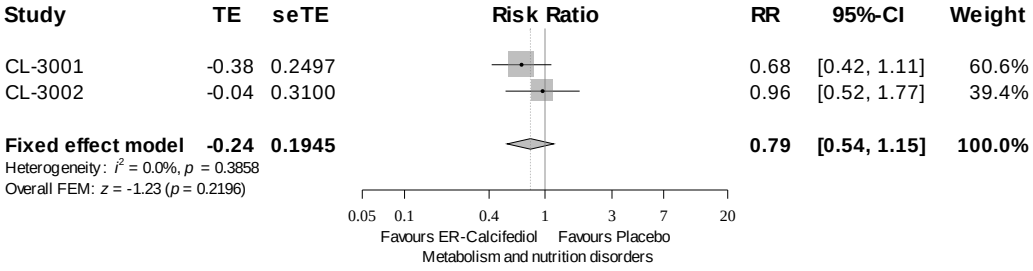
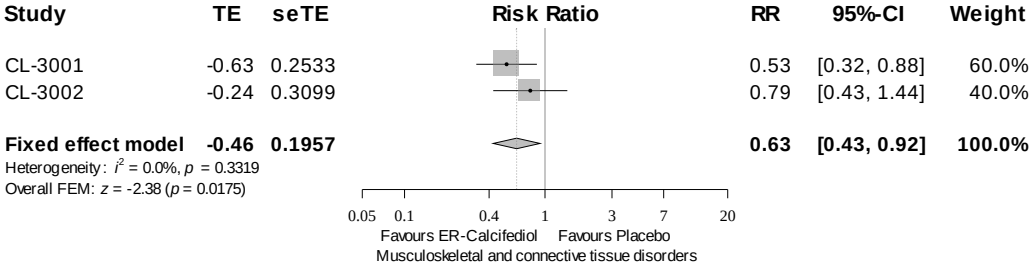
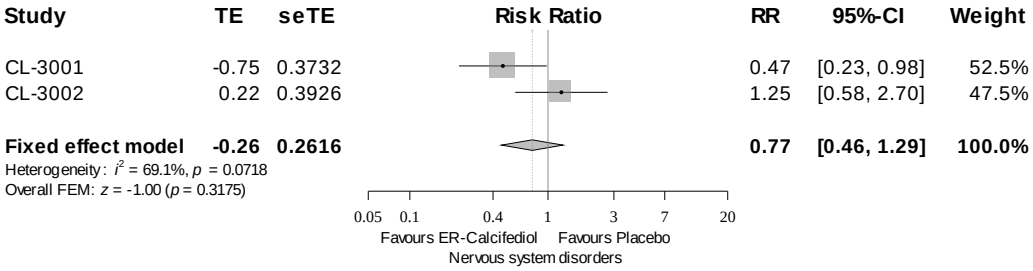


Figure 12.4.4.1.1 TEAE (independent of severity) Occurring ≥ 10% in One Arm by SOC
ITT Population









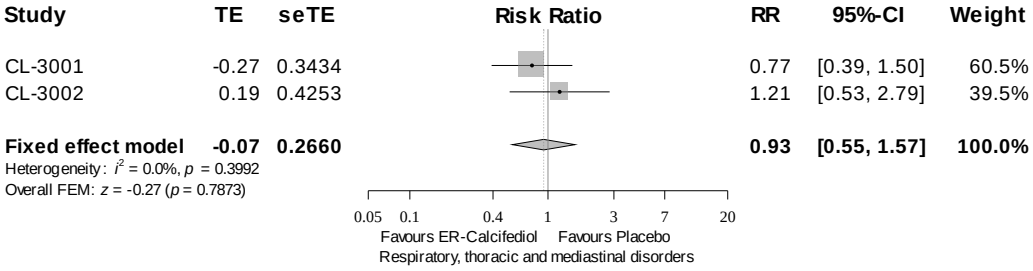
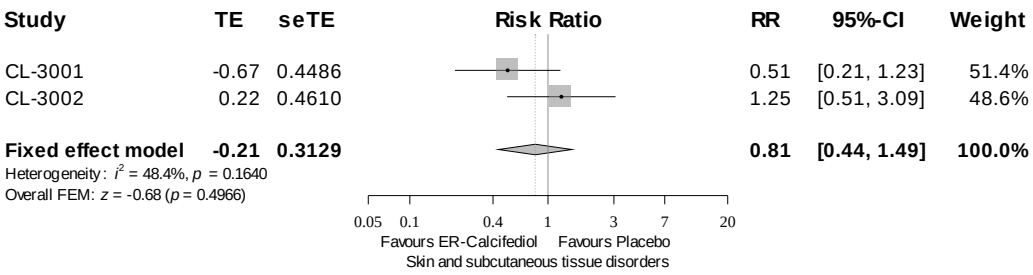


Figure 12.4.4.1.1 TEAE (independent of severity) Occurring ≥ 10% in One Arm by SOC ITT Population



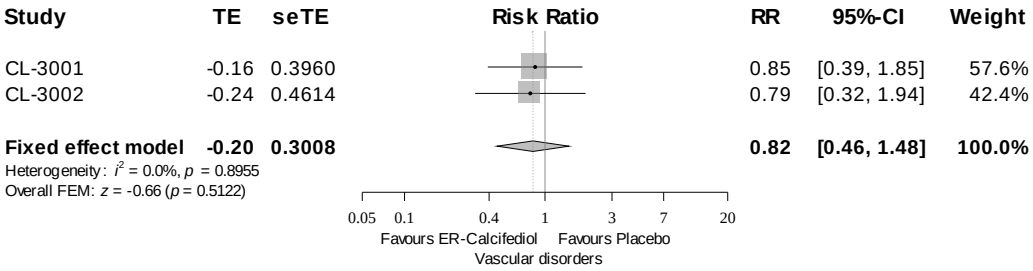
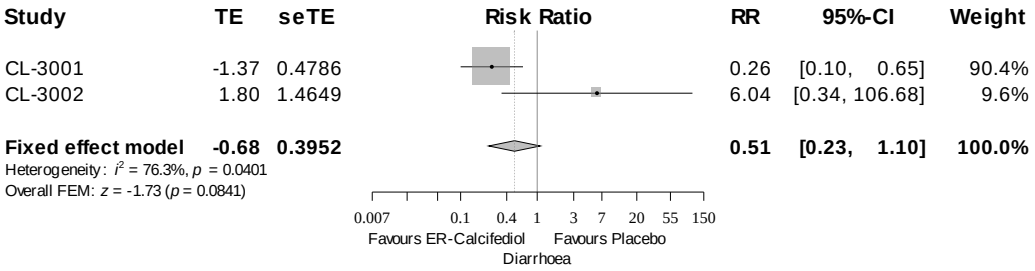


Figure 12.4.4.1.3 TEAE (independent of severity) Occurring ≥ 10% in One Arm by PT ITT Population



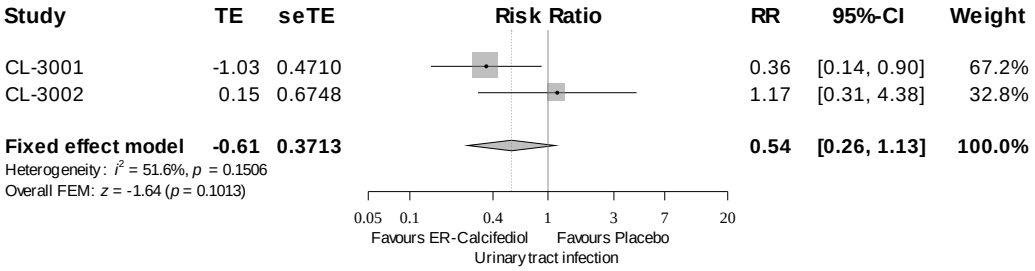
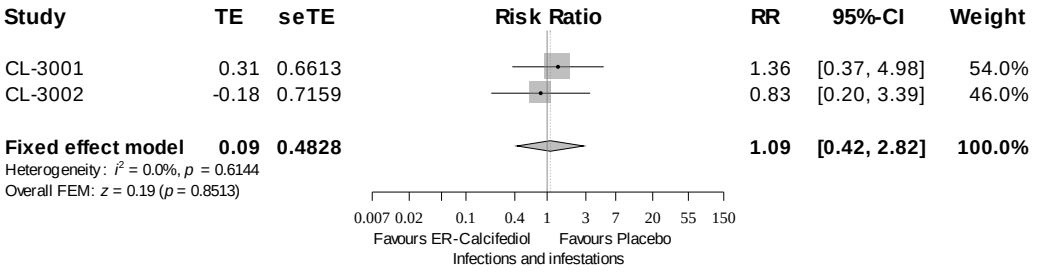


Figure 12.4.8.1.1 SAE Occurring ≥ 5% in One Arm by SOC
ITT Population



SAE Occurring ≥ 5% in One Arm by PT ITT Population

No SAE by PT occurred in at least 5% of patients in one treatment arm

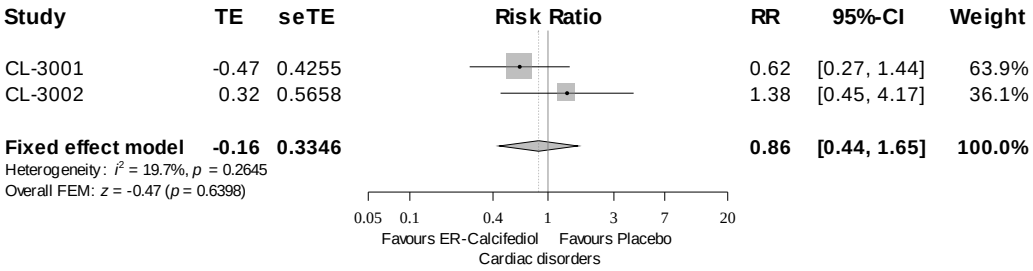
Severe AE Occurring ≥ 5% in One Arm by SOC ITT Population

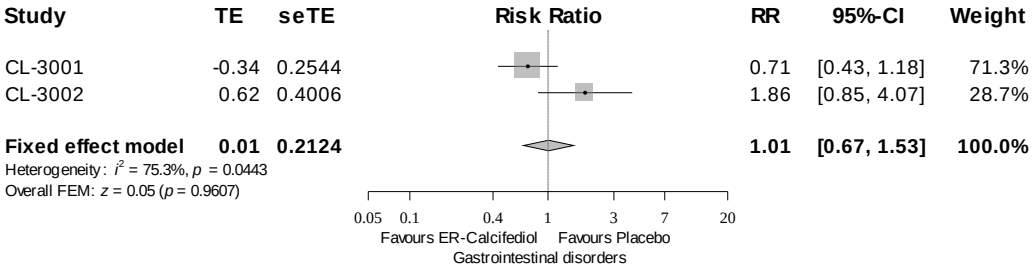
No severe AE by SOC occurred in at least 5% of patients in one treatment arm

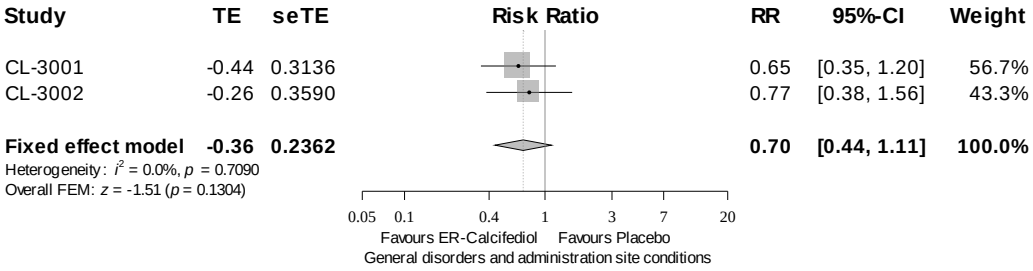
Severe AE Occurring ≥ 5% in One Arm by PT ITT Population

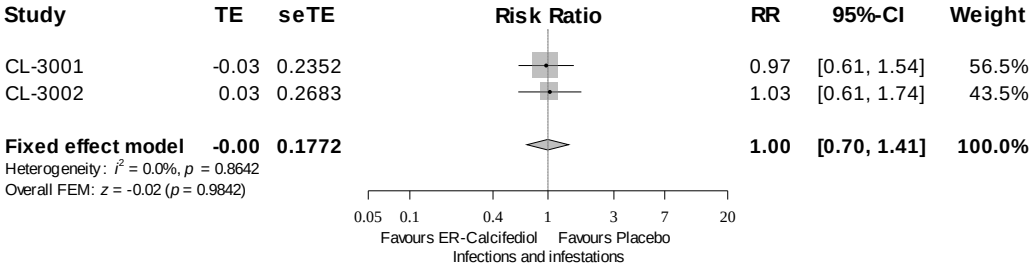
No severe AE by PT occurred in at least 5% of patients in one treatment arm

Figure 12.4.4.1.2 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC
ITT Population









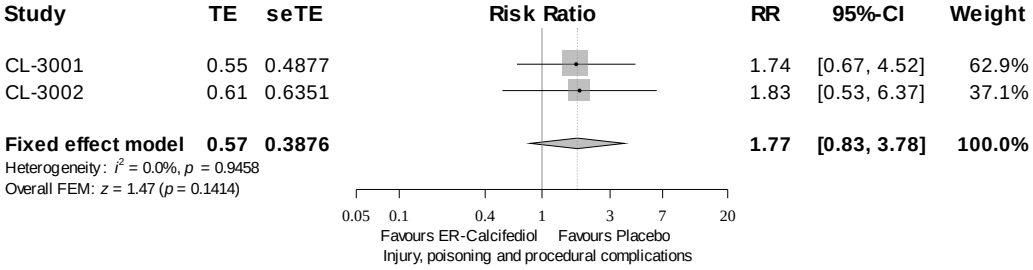
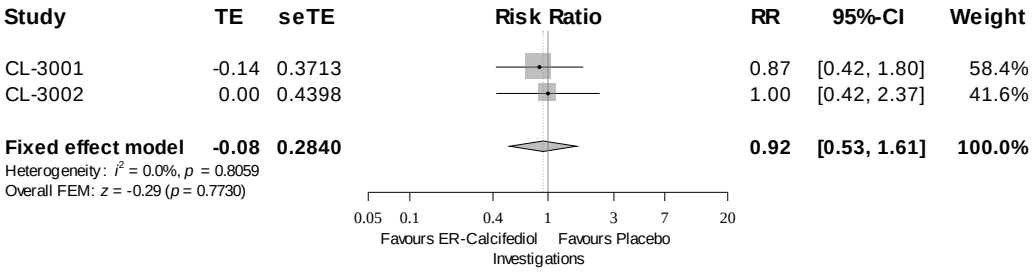
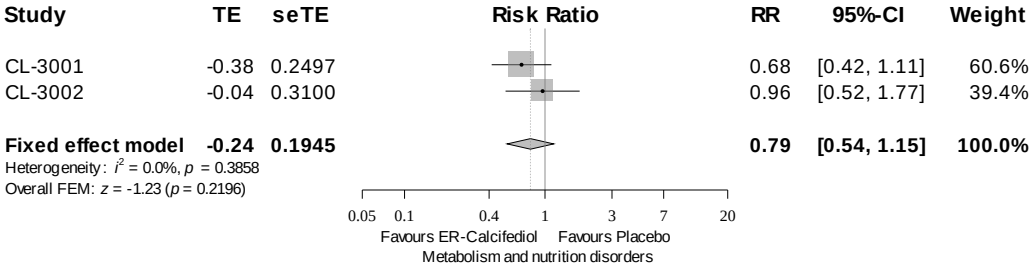
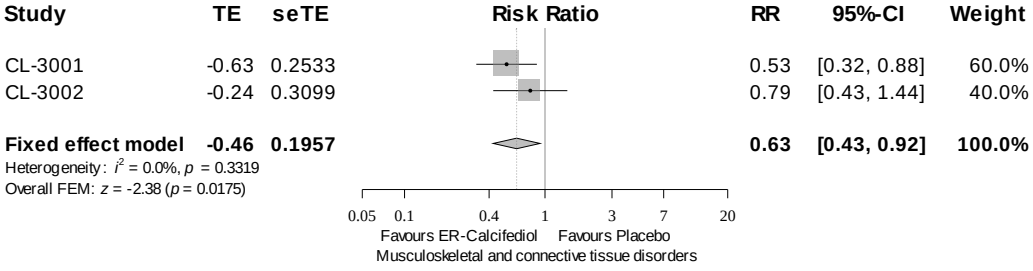
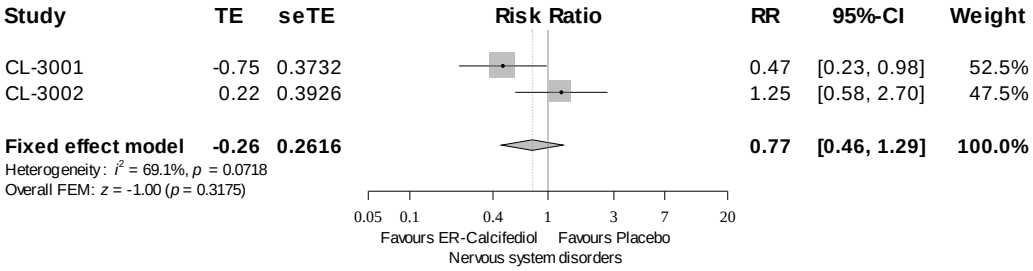


Figure 12.4.4.1.2 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC
ITT Population









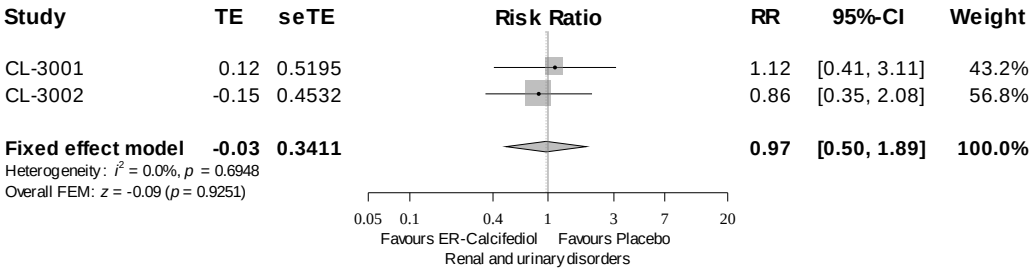
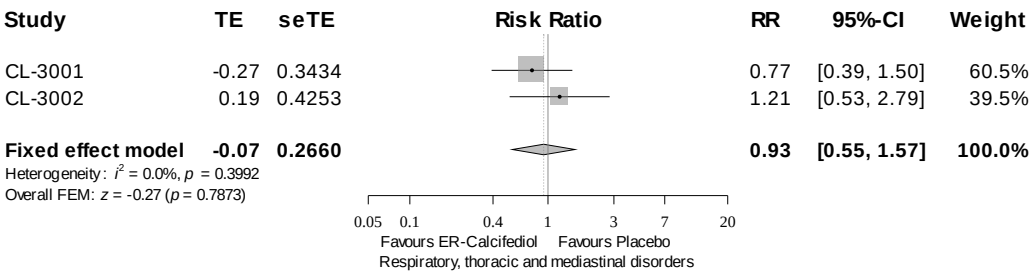
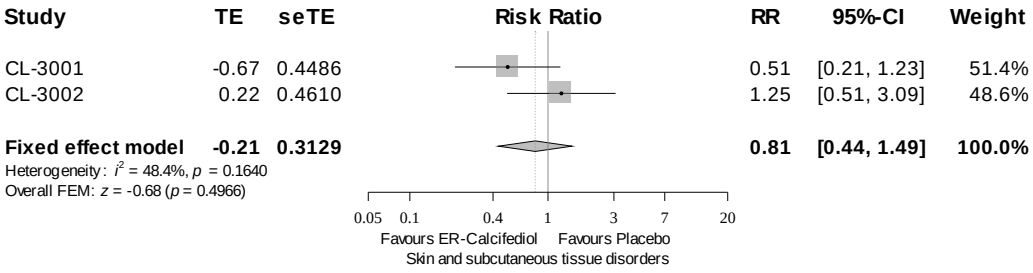


Figure 12.4.4.1.2 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC
ITT Population





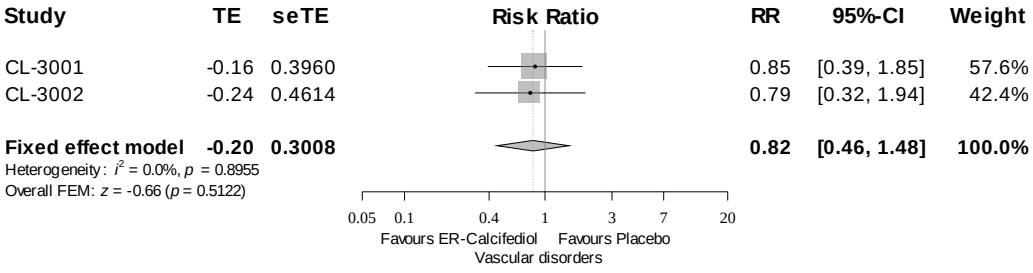
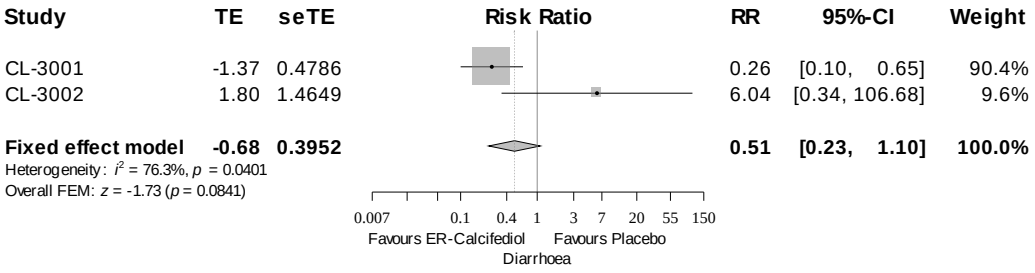
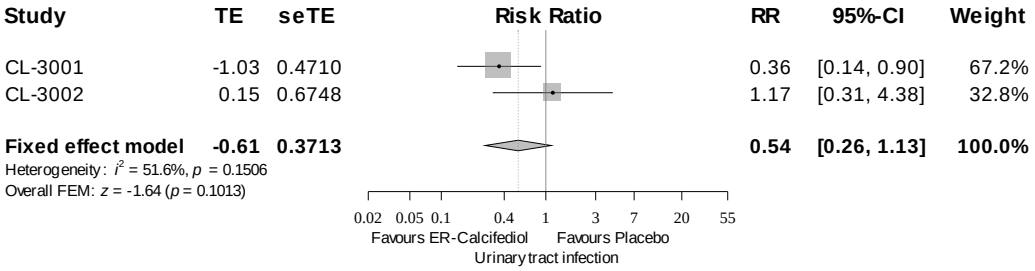


Figure 12.4.4.1.4 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by PT
ITT Population





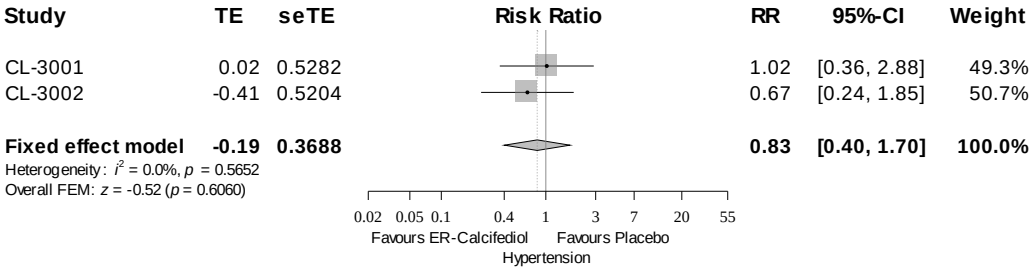
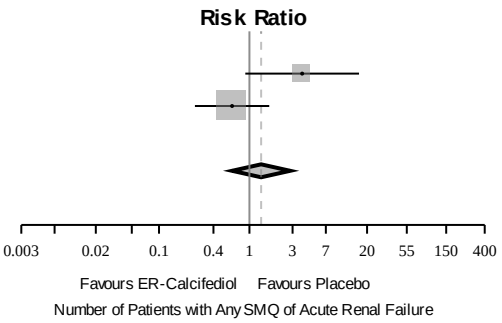


Figure 12.4.4.1.7 Summary of SMQs of Special Interest
ITT Population

Study	TE	seTE	RR	95%-CI	Weight
CL-3001	1.34	0.7387	3.83	[0.90, 16.29]	29.9%
CL-3002	-0.44	0.4828	0.64	[0.25, 1.66]	70.1%
Fixed effect model	**0.30**	**0.3773**	**1.35**	**[0.64, 2.82]**	**100.0%**

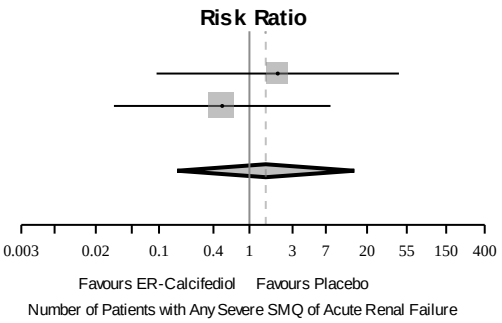
Heterogeneity: i^2 = 75.5%, p = 0.0432
Overall FEM: z = 0.79 (p = 0.4293)



Number of Patients with Any SMQ of Acute Renal Failure

Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.72	1.5745	2.06	[0.09, 45.02]	44.4%
CL-3002	-0.69	1.4068	0.50	[0.03, 7.88]	55.6%
Fixed effect model	**0.42**	**0.9948**	**1.52**	**[0.16, 14.44]**	**100.0%**

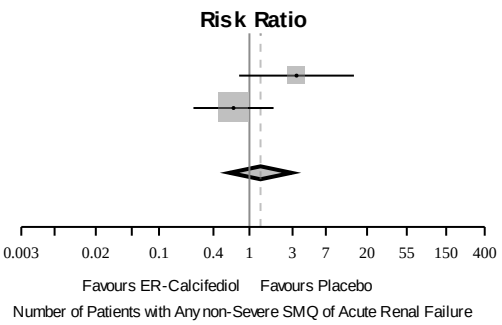
Heterogeneity: i^2 = 0.0%, p = 0.5030
Overall FEM: z = 0.36 (p = 0.7176)



Number of Patients with Any Severe SMQ of Acute Renal Failure

Study	TE	seTE	RR	95%-CI	Weight
CL-3001	1.20	0.7456	3.32	[0.77, 14.31]	32.8%
CL-3002	-0.41	0.5204	0.67	[0.24, 1.85]	67.2%
Fixed effect model	**0.28**	**0.4027**	**1.33**	**[0.60, 2.92]**	**100.0%**

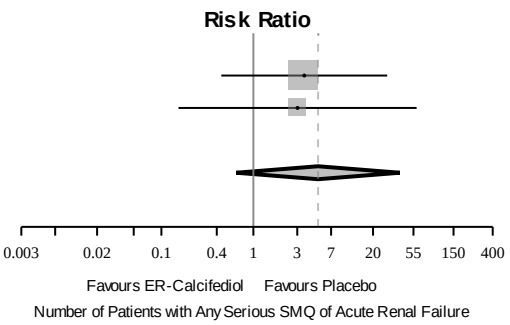
Heterogeneity: i^2 = 67.9%, p = 0.0775
Overall FEM: z = 0.70 (p = 0.4831)



Number of Patients with Any non-Severe SMQ of Acute Renal Failure

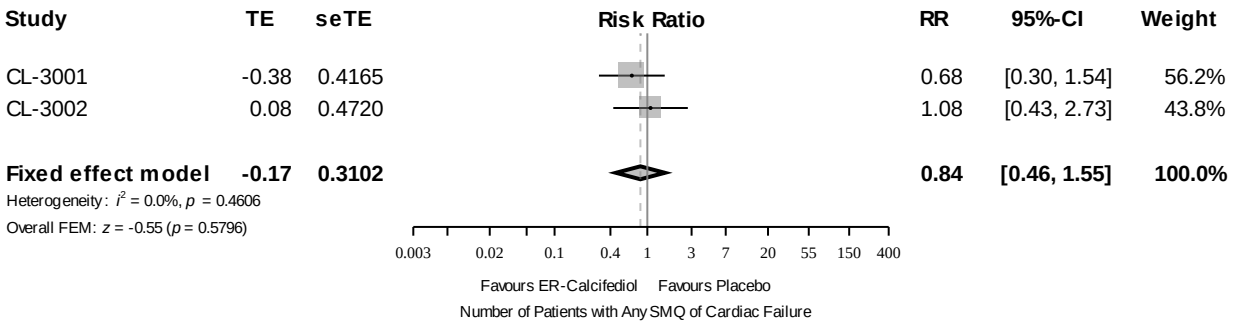
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	1.27	1.0592	3.57	[0.45, 28.50]	67.3%
CL-3002	1.11	1.5207	3.02	[0.15, 59.51]	32.7%
Fixed effect model	**1.62**	**0.8696**	**5.05**	**[0.65, 39.09]**	**100.0%**

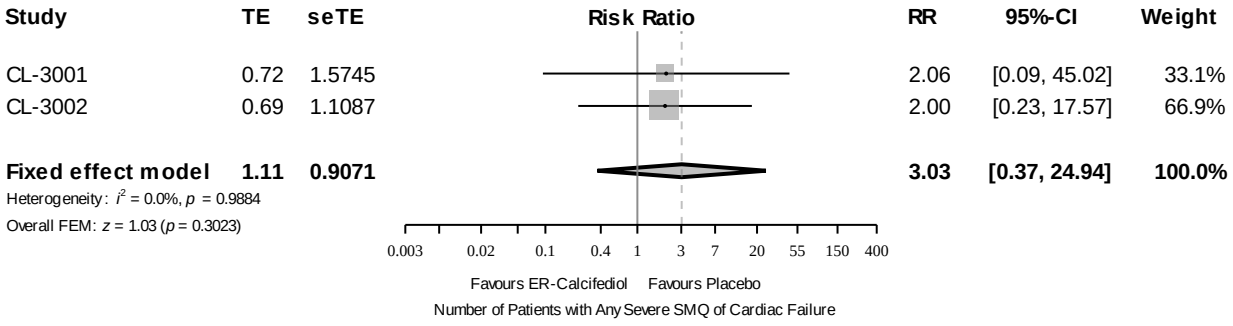
Heterogeneity: i^2 = 0.0%, p = 0.9276
Overall FEM: z = 1.55 (p = 0.1207)

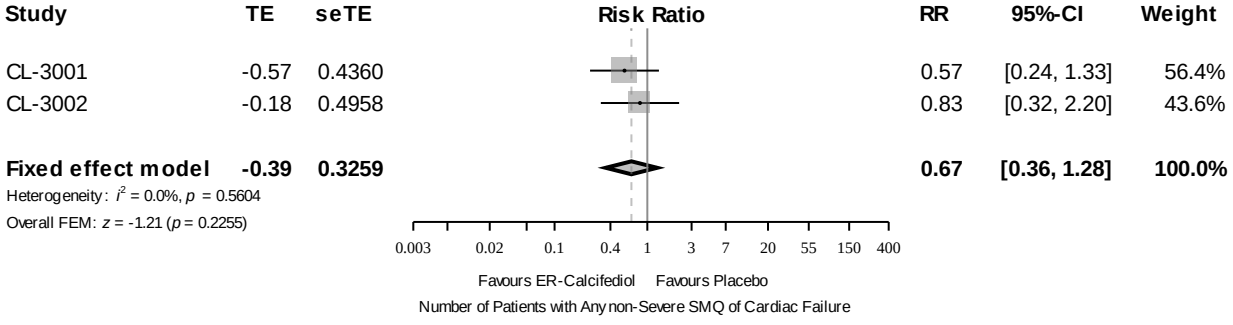


Number of Patients with Any Serious SMQ of Acute Renal Failure

Figure 12.4.4.1.7 Summary of SMQs of Special Interest
ITT Population







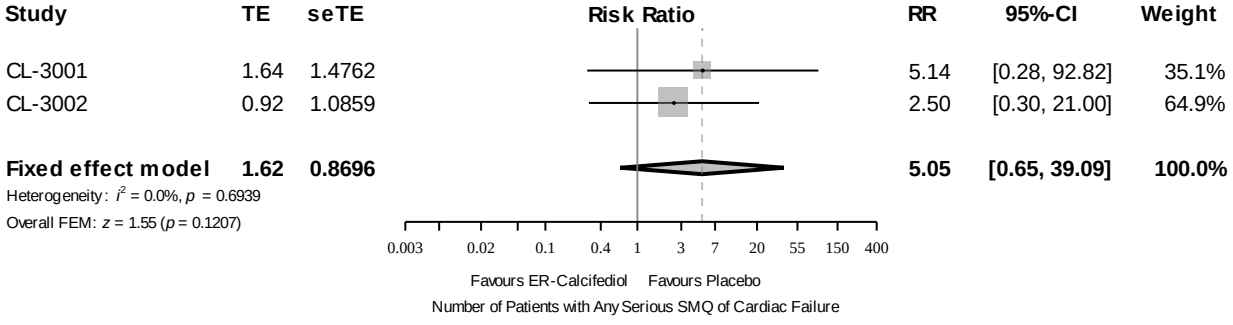
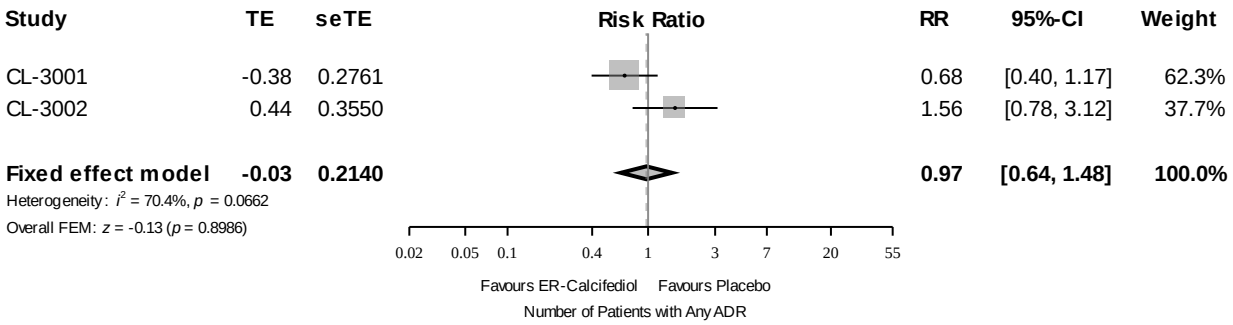
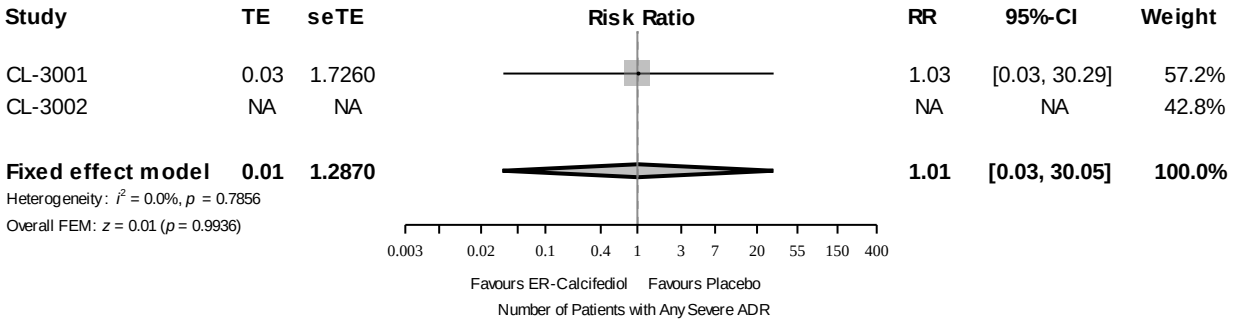
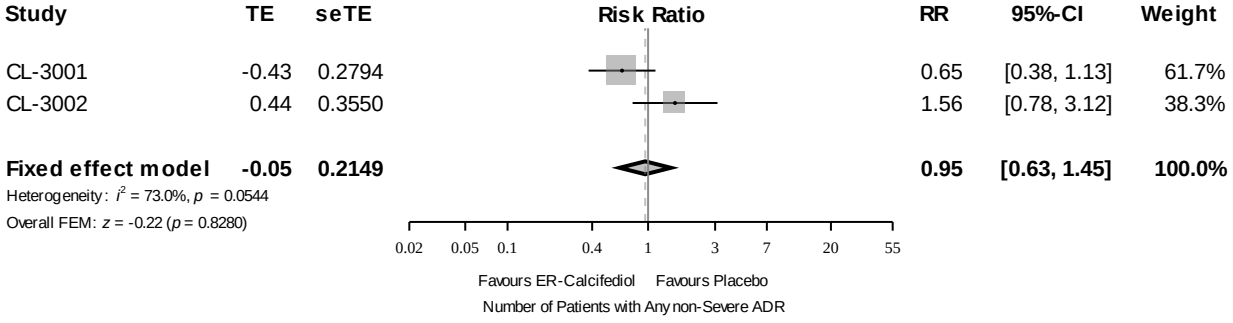
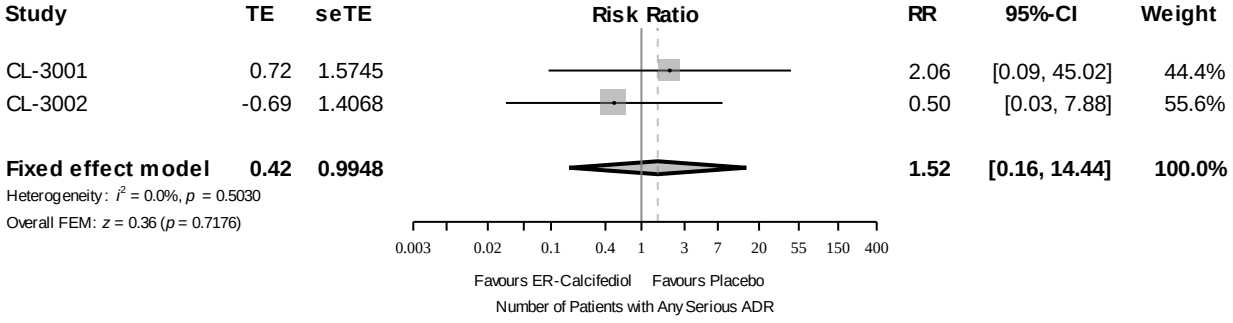


Figure 12.4.4.1.6 Summary of ADRs
ITT Population









Nachberechnungsdokument
Forest Plots - Sicherheitsendpunkte
Unerwünschte Ereignisse
(PP-Population)

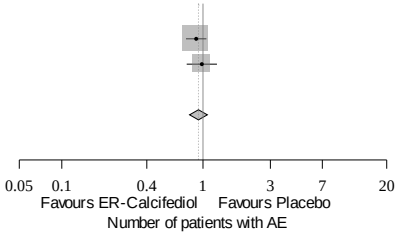
Folgende Daten werden für die PP-Population dargestellt:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (SMQs)
  - UE ohne erkrankungsbezogene Ereignisse

Figure 12.4.3.1.s10 Summary of TEAE
PP Population

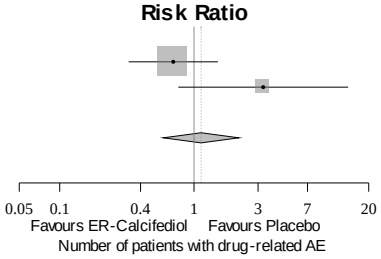
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.11	0.0850	0.89	[0.76, 1.06]	68.7%
CL-3002	-0.02	0.1259	0.98	[0.77, 1.26]	31.3%
Fixed effect model	**-0.07**	**0.0740**	**0.93**	**[0.80, 1.07]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.5449
Overall FEM: z = -1.00 (p = 0.3187)



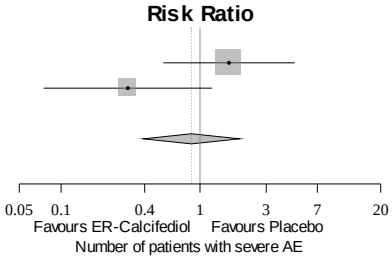
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.36	0.3900	0.70	[0.33, 1.51]	78.4%
CL-3002	1.19	0.7429	3.28	[0.76, 14.06]	21.6%
Fixed effect model	**0.12**	**0.3306**	**1.13**	**[0.59, 2.16]**	**100.0%**

Heterogeneity: I^2 = 70.4%, p = 0.0660
Overall FEM: z = 0.37 (p = 0.7124)



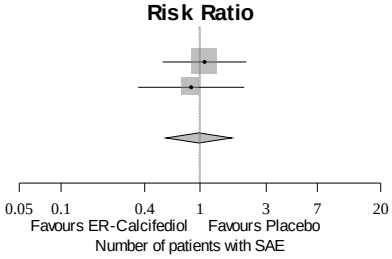
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.48	0.5554	1.62	[0.54, 4.80]	62.2%
CL-3002	-1.20	0.7129	0.30	[0.07, 1.22]	37.8%
Fixed effect model	**-0.14**	**0.4066**	**0.87**	**[0.39, 1.93]**	**100.0%**

Heterogeneity: I^2 = 70.9%, p = 0.0636
Overall FEM: z = -0.35 (p = 0.7297)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.08	0.3538	1.08	[0.54, 2.16]	61.6%
CL-3002	-0.15	0.4485	0.86	[0.36, 2.08]	38.4%
Fixed effect model	**-0.02**	**0.2786**	**0.98**	**[0.57, 1.69]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.6987
Overall FEM: z = -0.07 (p = 0.9463)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.36	0.6584	1.44	[0.40, 5.23]	83.4%
CL-3002	1.63	1.4748	5.08	[0.28, 91.53]	16.6%
Fixed effect model	**0.82**	**0.6307**	**2.26**	**[0.66, 7.78]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.4342
Overall FEM: z = 1.29 (p = 0.1963)

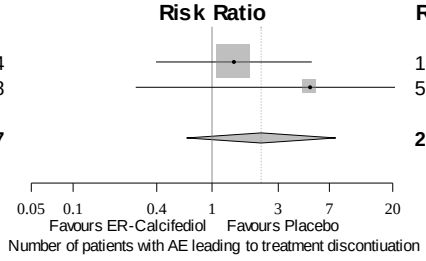
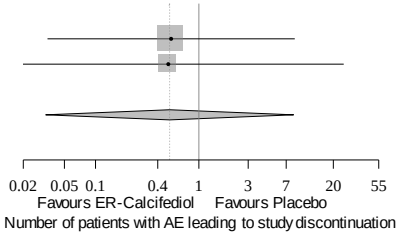


Figure 12.4.3.1.s10 Summary of TEAE
PP Population

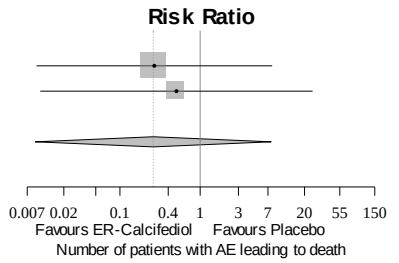
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.62	1.4054	0.54	[0.03, 8.47]	66.8%
CL-3002	-0.68	1.9938	0.51	[0.01, 25.20]	33.2%
Fixed effect model	**-0.65**	**1.4098**	**0.52**	**[0.03, 8.26]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.9794
Overall FEM: z = -0.46 (p = 0.6441)



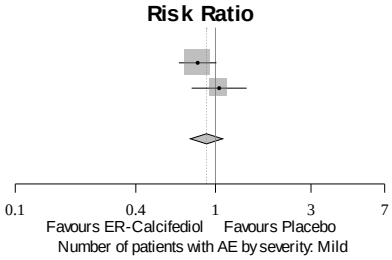
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-1.32	1.7249	0.27	[0.01, 7.89]	57.2%
CL-3002	-0.68	1.9938	0.51	[0.01, 25.20]	42.8%
Fixed effect model	**-1.35**	**1.7284**	**0.26**	**[0.01, 7.70]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.8098
Overall FEM: z = -0.78 (p = 0.4359)



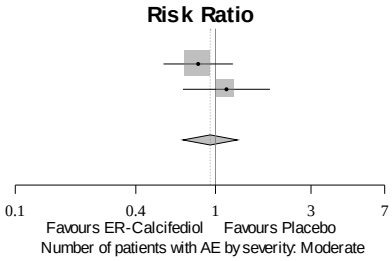
Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.20	0.1100	0.81	[0.66, 1.01]	68.3%
CL-3002	0.04	0.1615	1.04	[0.76, 1.43]	31.7%
Fixed effect model	**-0.10**	**0.0941**	**0.90**	**[0.75, 1.08]**	**100.0%**

Heterogeneity: I^2 = 37.5%, p = 0.2058
Overall FEM: z = -1.10 (p = 0.2722)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	-0.20	0.2037	0.82	[0.55, 1.22]	61.1%
CL-3002	0.13	0.2554	1.13	[0.69, 1.87]	38.9%
Fixed effect model	**-0.06**	**0.1595**	**0.94**	**[0.69, 1.29]**	**100.0%**

Heterogeneity: I^2 = 0.0%, p = 0.3194
Overall FEM: z = -0.38 (p = 0.7030)



Study	TE	seTE	RR	95%-CI	Weight
CL-3001	0.48	0.5554	1.62	[0.54, 4.80]	62.2%
CL-3002	-1.20	0.7129	0.30	[0.07, 1.22]	37.8%
Fixed effect model	**-0.14**	**0.4066**	**0.87**	**[0.39, 1.93]**	**100.0%**

Heterogeneity: I^2 = 70.9%, p = 0.0636
Overall FEM: z = -0.35 (p = 0.7297)

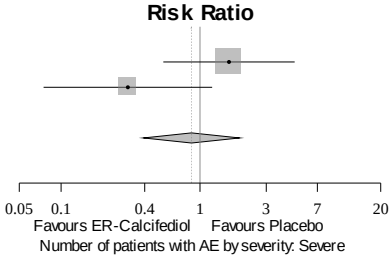


Figure 12.4.4.1.1.s10 TEAE (independent of severity) Occurring ≥ 10% in One Arm by SOC PP Population

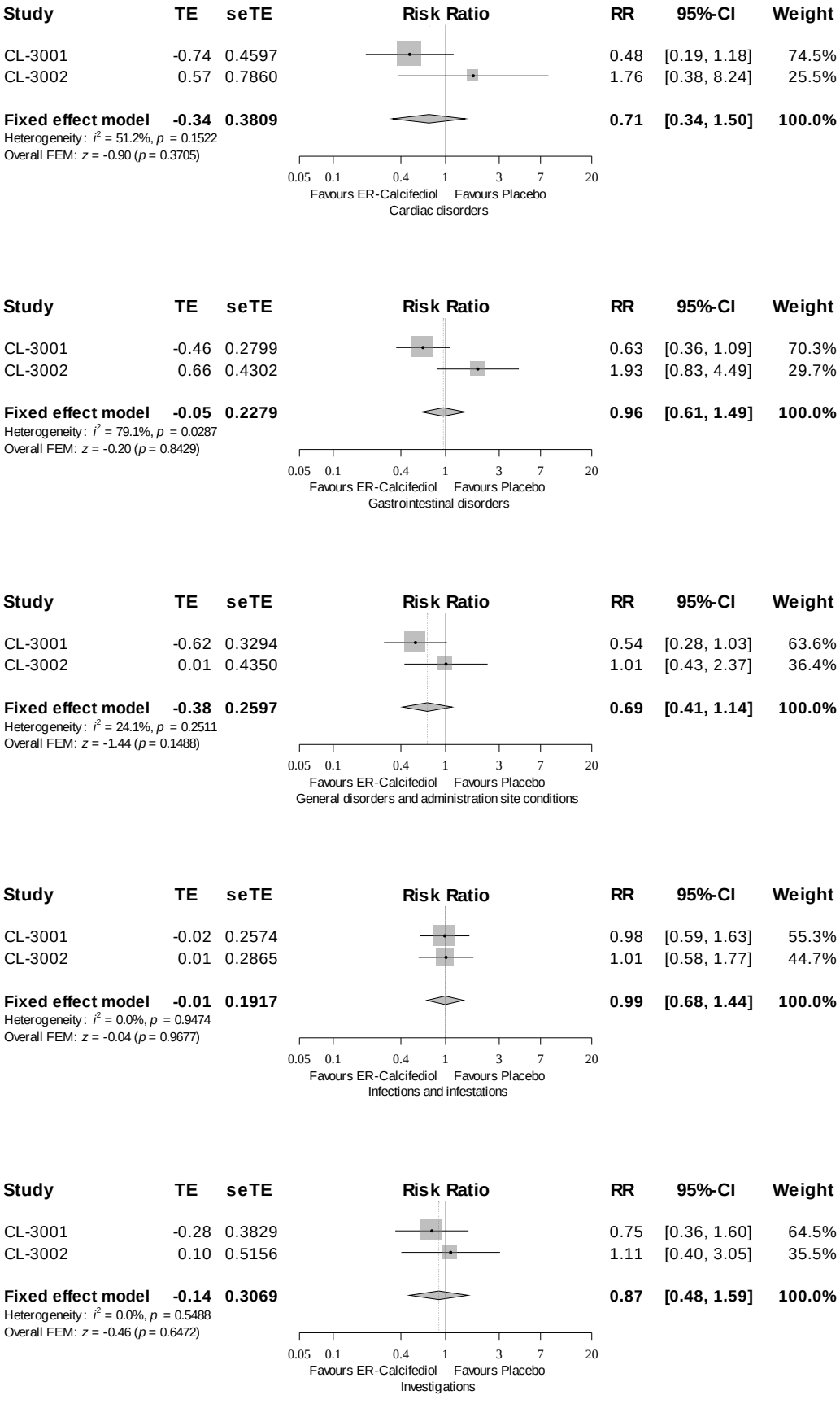
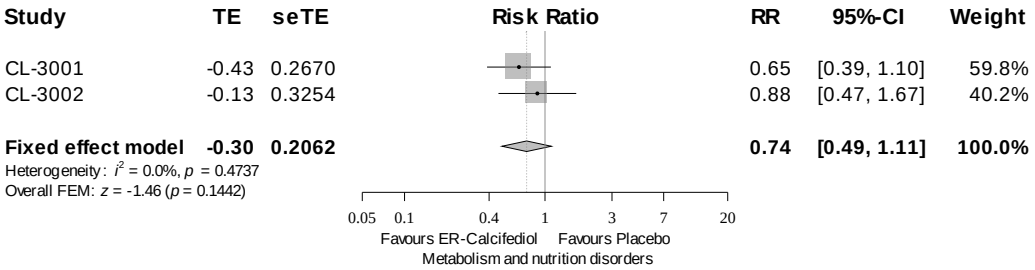
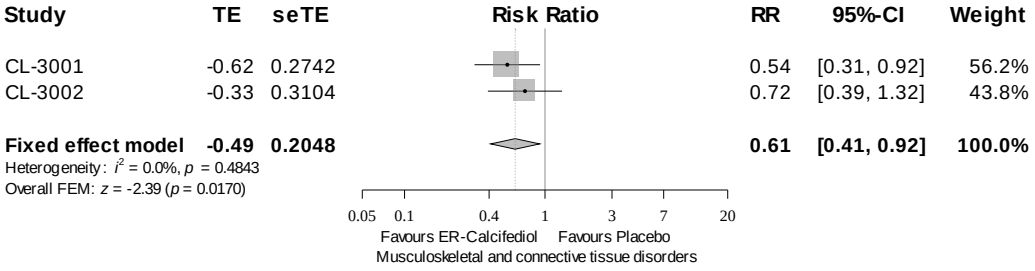
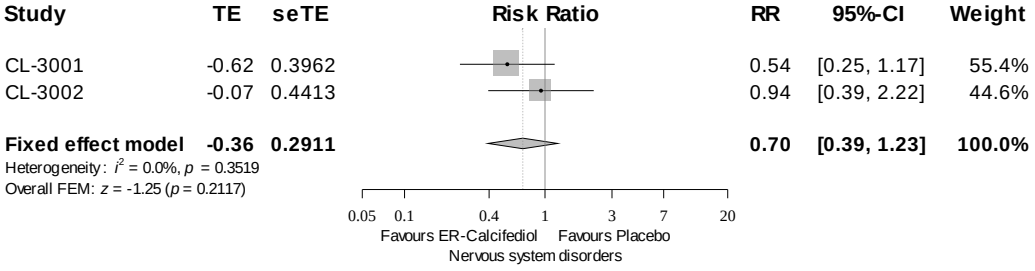
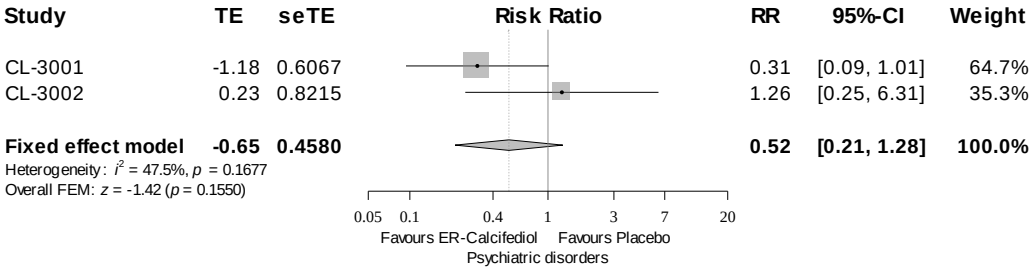


Figure 12.4.4.1.1.s10 TEAE (independent of severity) Occurring ≥ 10% in One Arm by SOC
PP Population









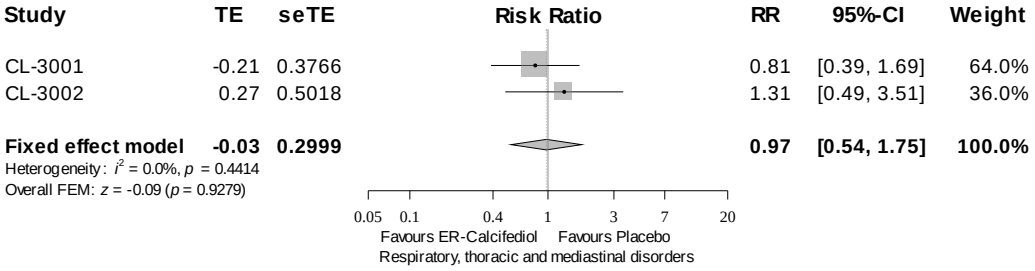
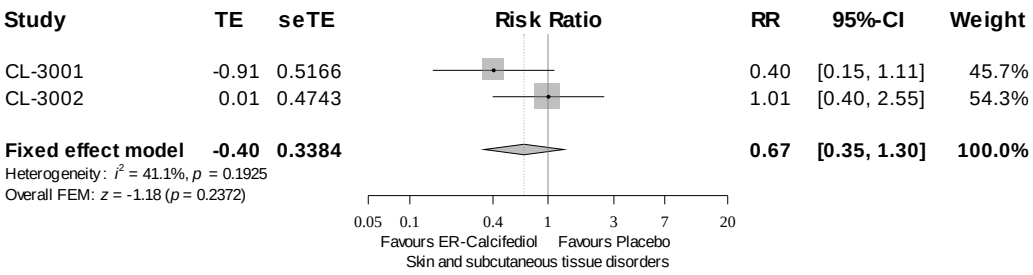


Figure 12.4.4.1.1.s10 TEAE (independent of severity) Occurring ≥ 10% in One Arm by SOC
PP Population



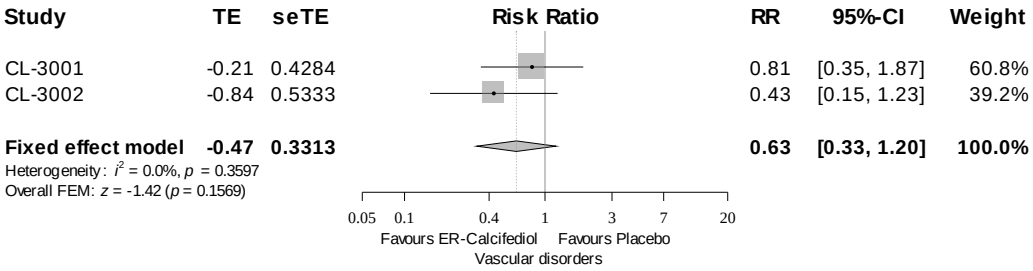
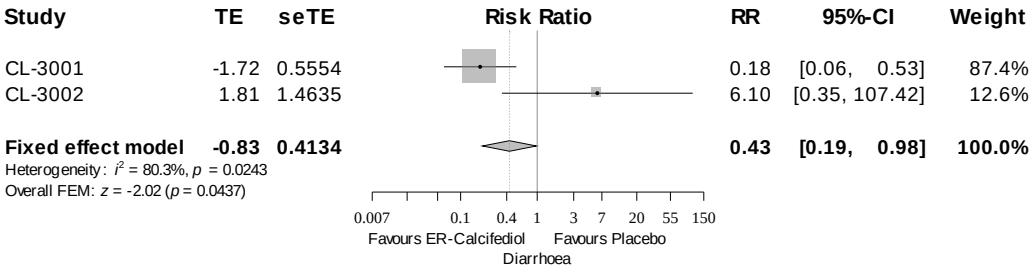
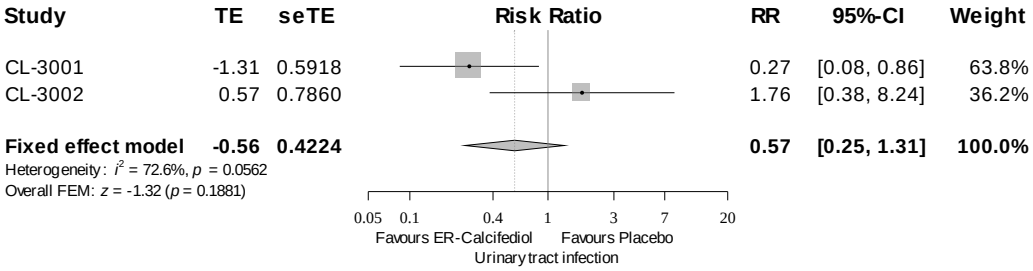


Figure 12.4.4.1.3.s10 TEAE (independent of severity) Occurring ≥ 10% in One Arm by PT
PP Population





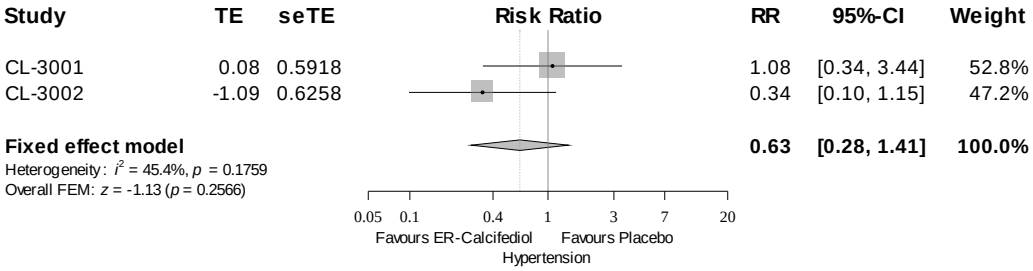
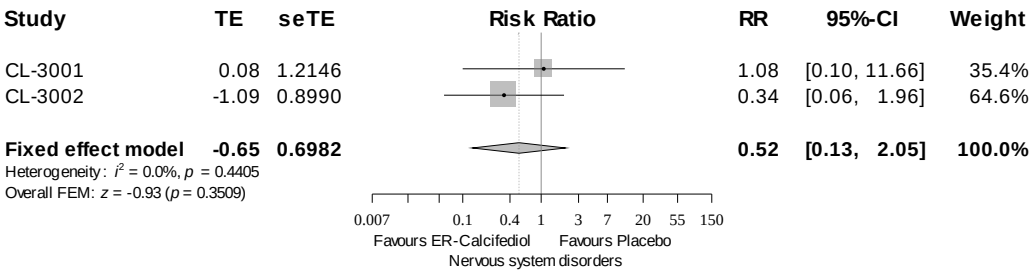


Figure 12.4.8.1.1.s10 SAE Occurring ≥ 5% in One Arm by SOC
PP Population



SAE Occurring ≥ 5% in One Arm by PT PP Population

No SAE by PT occurred in at least 5% of patients in one treatment arm

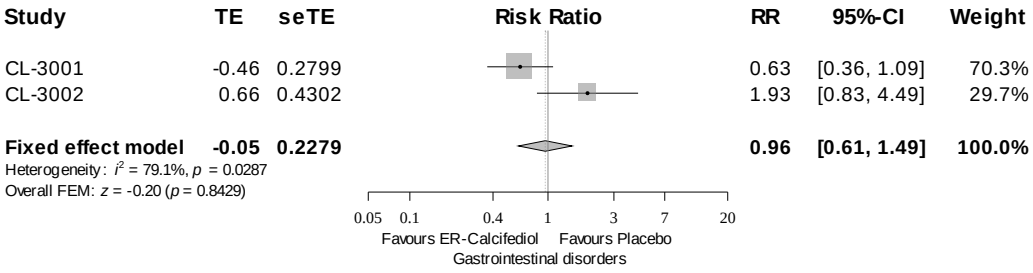
Severe AE Occurring ≥ 5% in One Arm by SOC PP Population

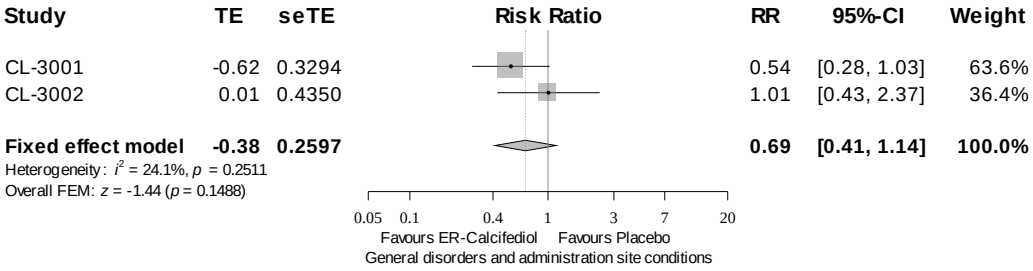
No severe AE by SOC occurred in at least 5% of patients in one treatment arm

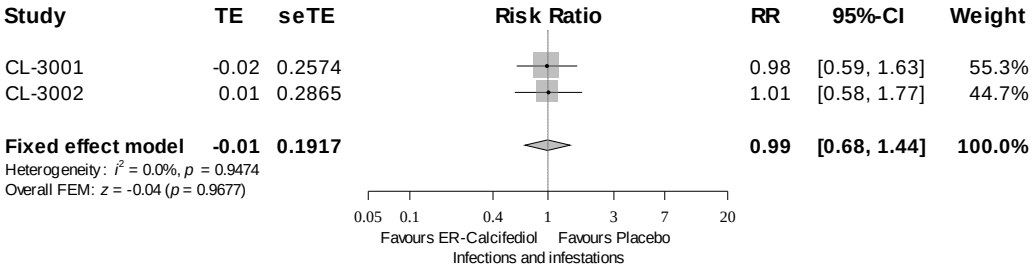
Severe AE Occurring ≥ 5% in One Arm by PT PP Population

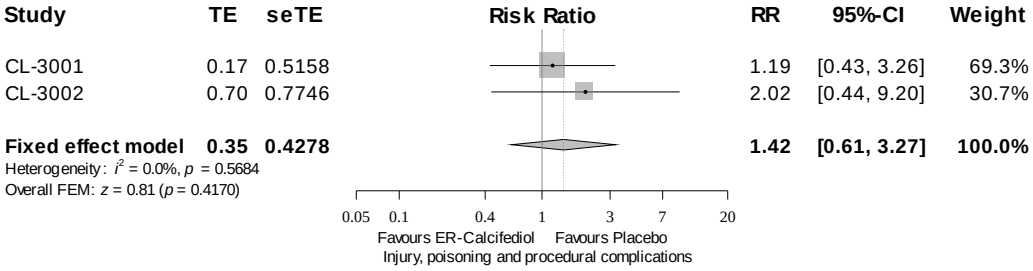
No severe AE by PT occurred in at least 5% of patients in one treatment arm

Figure 12.4.4.1.2.s10 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC
PP Population









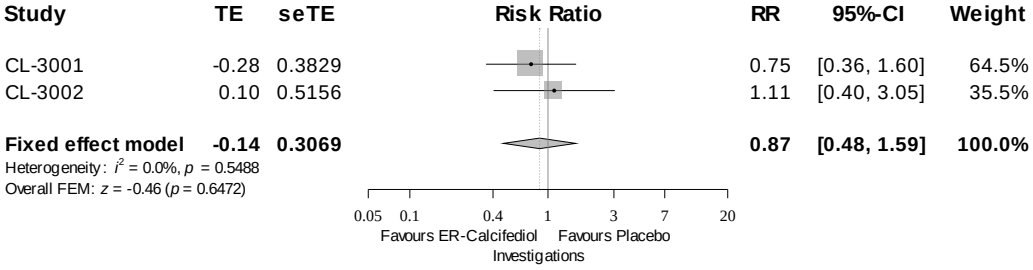
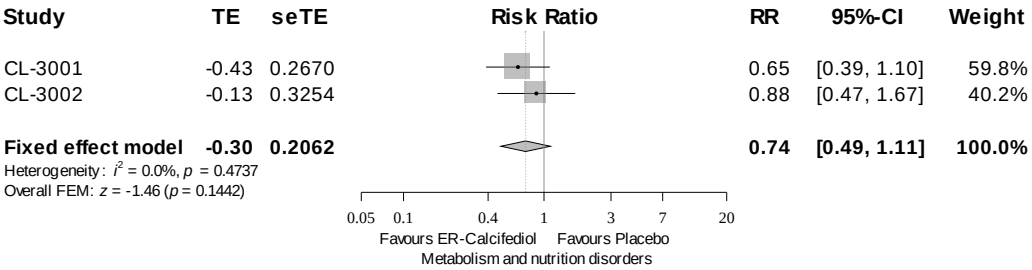
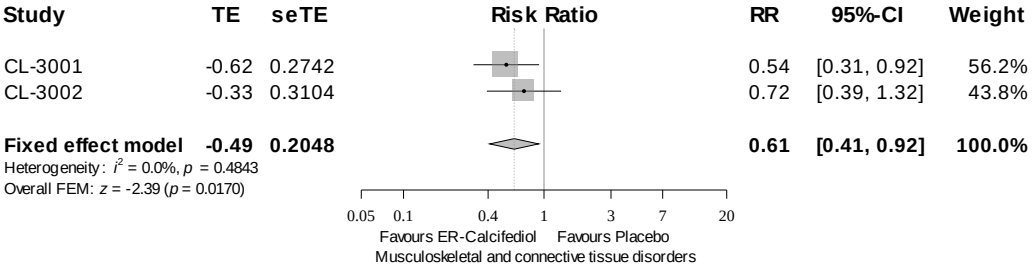
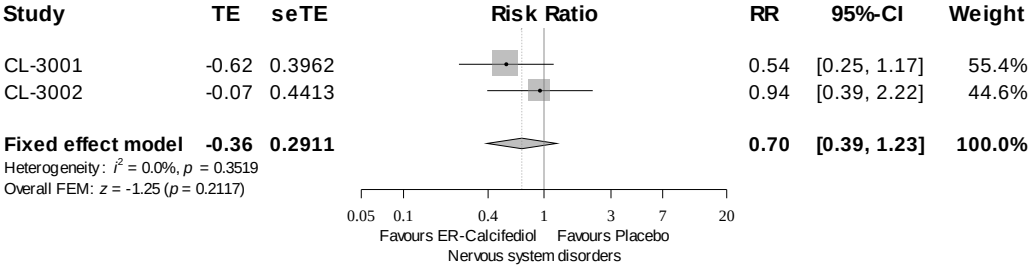
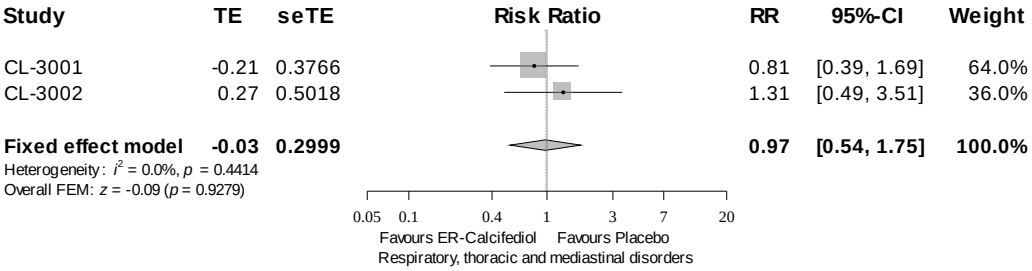


Figure 12.4.4.1.2.s10 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC PP Population









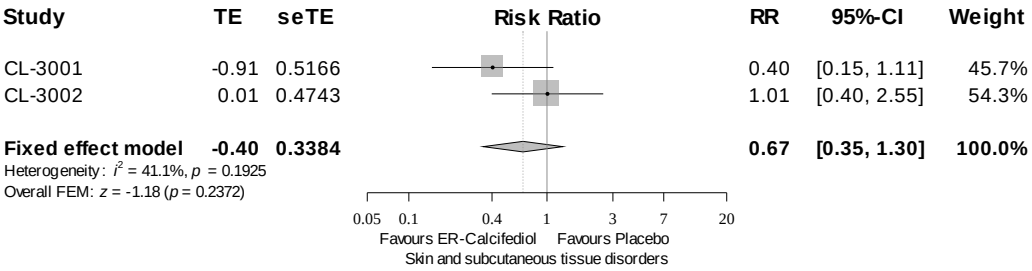


Figure 12.4.4.1.2.s10 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by SOC PP Population

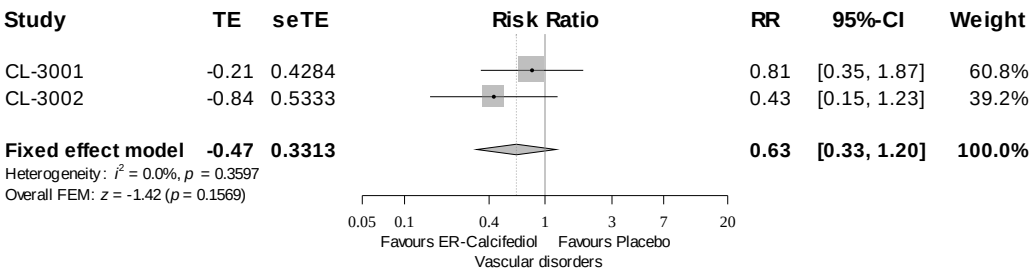


Figure 12.4.4.1.4.s10 TEAE (independent of severity) Occurring ≥ 10 Patients AND ≥ 1% in One Arm by PT
PP Population

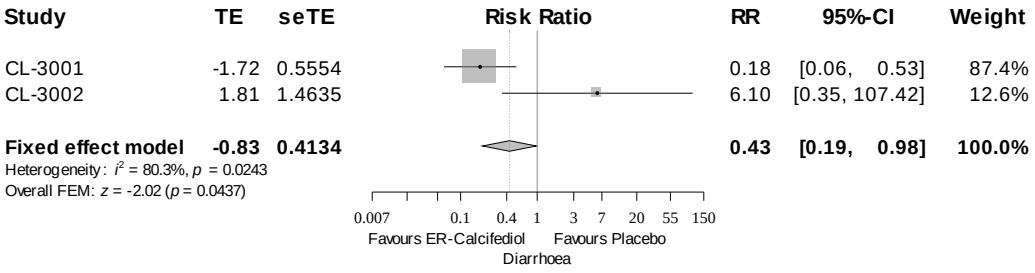
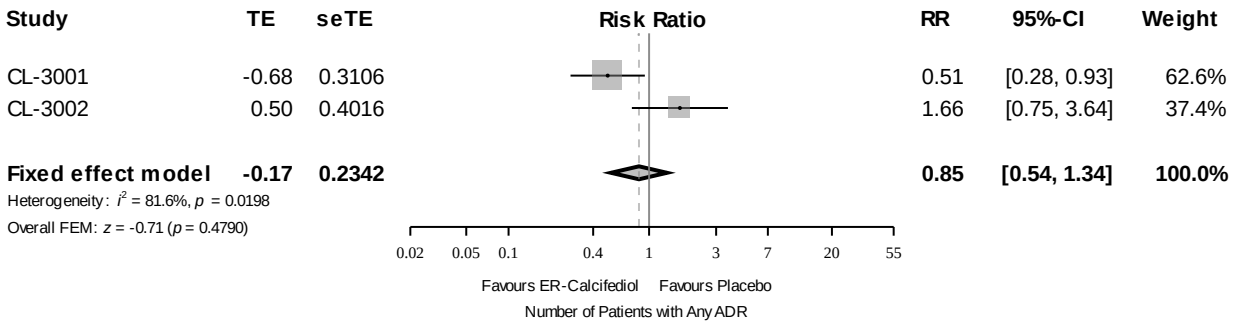
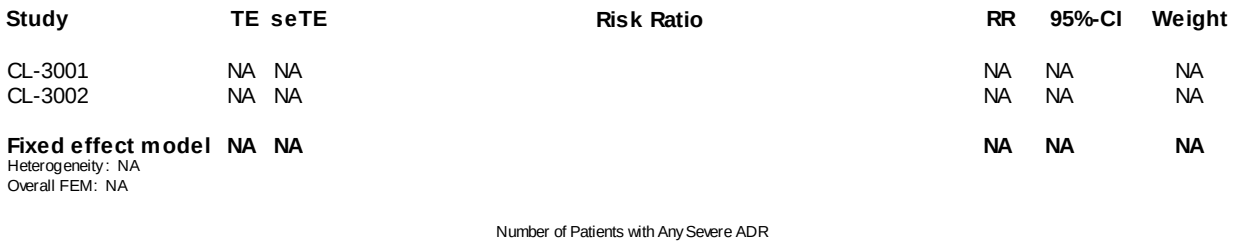
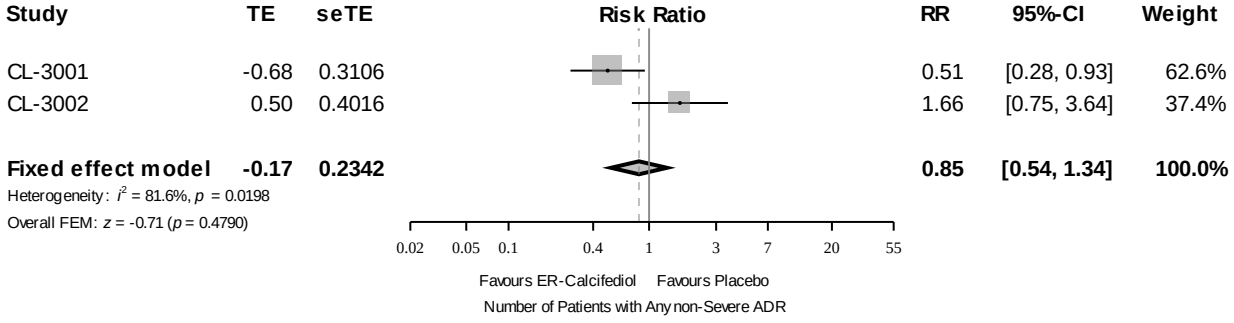


Figure 12.4.4.1.6.s10 Summary of ADRs
PP Population







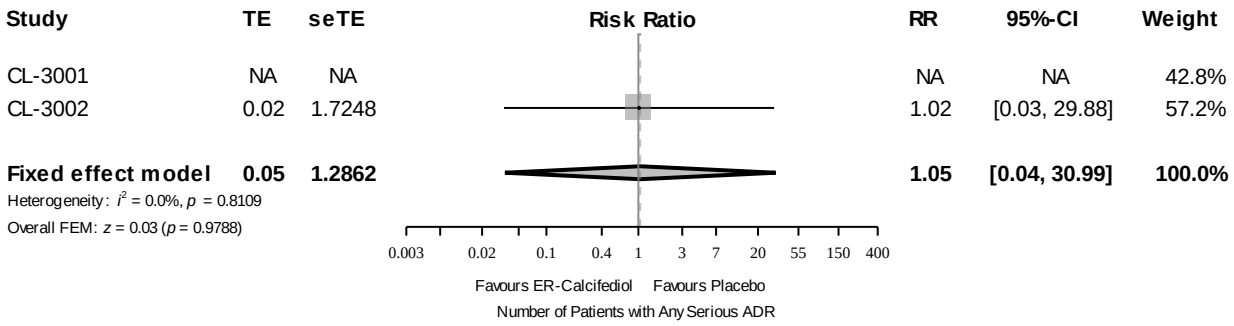
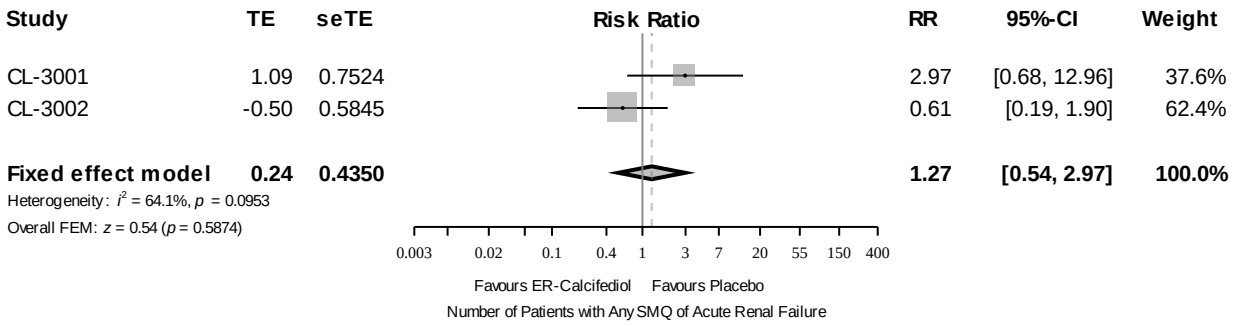
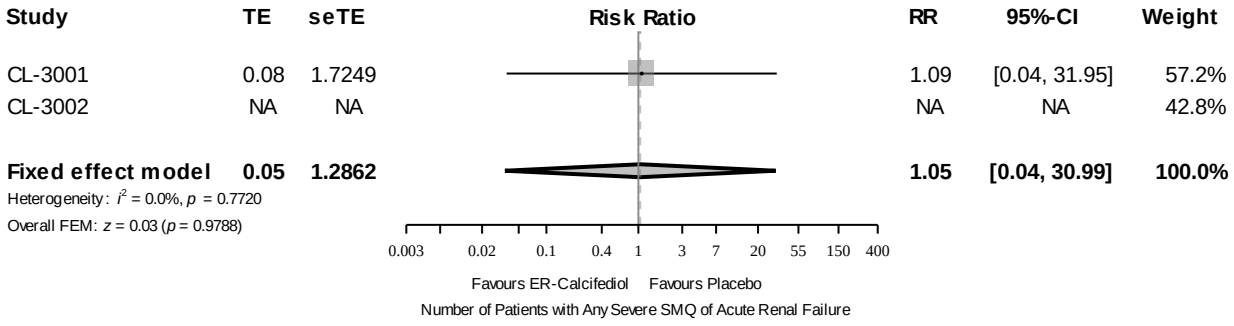
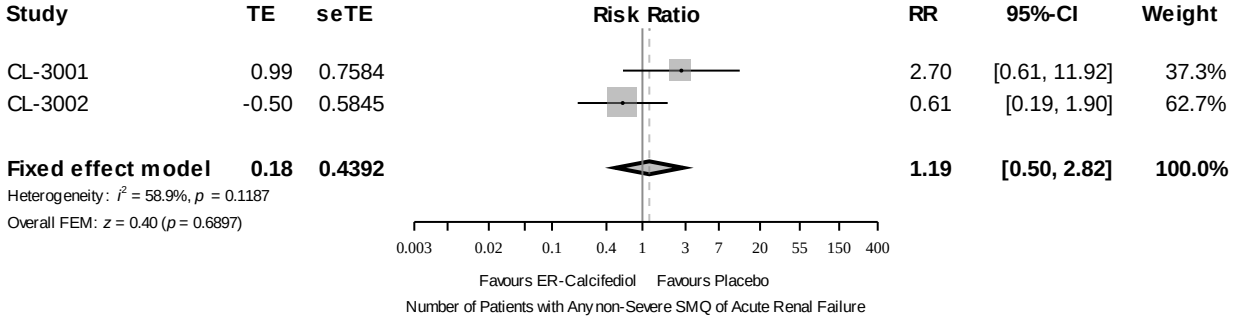


Figure 12.4.4.1.7.s10 Summary of SMQs of Special Interest
PP Population







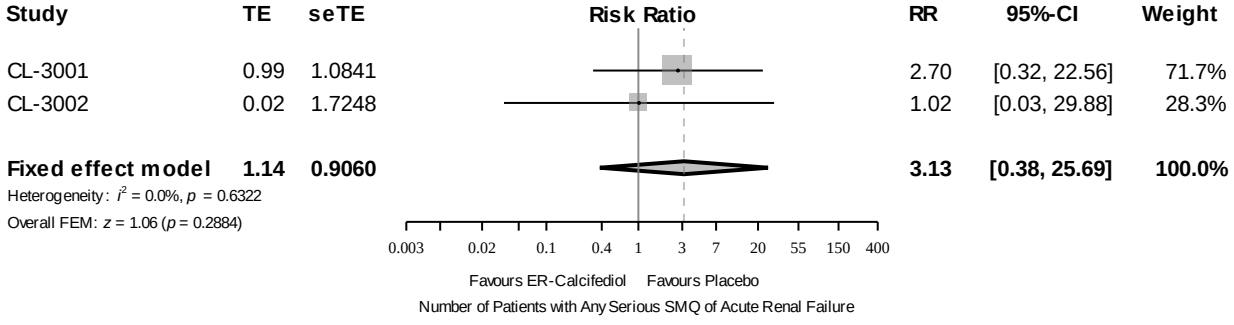
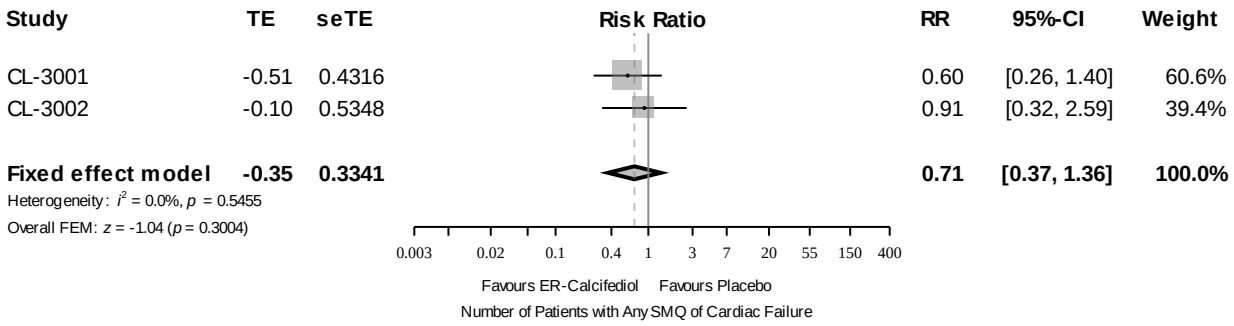
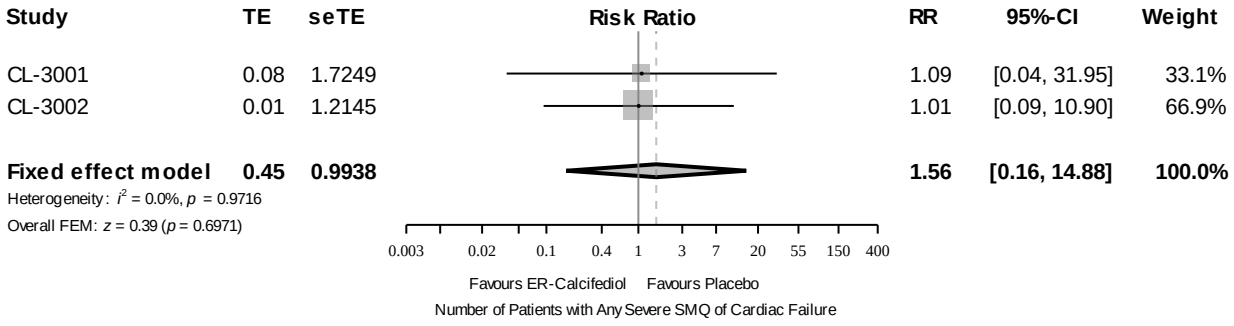
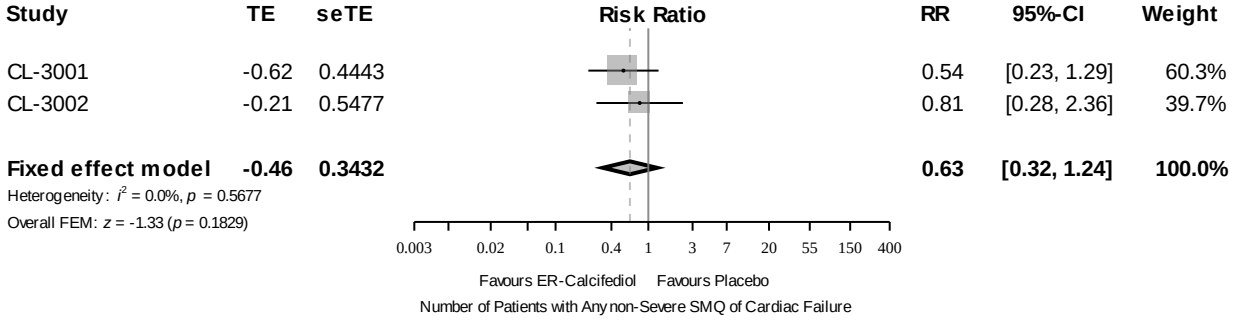
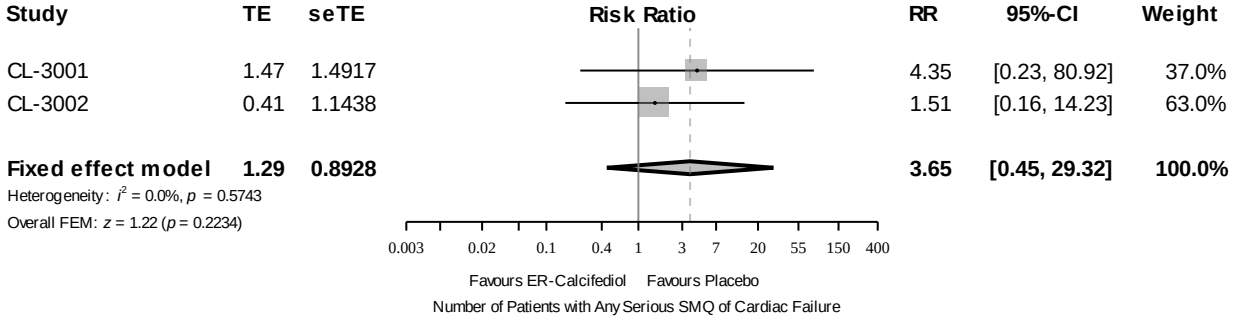


Figure 12.4.4.1.7.s10 Summary of SMQs of Special Interest
PP Population









Nachberechnungsdokument Subgruppenanalysen - Wirksamkeitsendpunkte (ITT-Population)

Folgende Daten werden für die ITT-Population

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einemm 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2267		0.1472		0.0581	
Comparison Baseline vs. EAP	0.4516		0.0409		0.0461	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	150.3 (61.55)	136.7 (42.85)	163.2 (77.79)	171.4 (80.13)	156.2 (69.43)	154.6 (66.65)
Visit 13/ET						
n/N1	56/59	30/30	46/50	28/32	102/109	58/62
Mean (SD)	119.0 (65.24)	141.1 (57.39)	127.5 (113.44)	180.4 (99.16)	122.8 (89.83)	160.1 (82.02)
EAP						
n/N1	52/59	30/30	42/50	26/32	94/109	56/62
Mean (SD)	113.6 (48.64)	144.7 (59.34)	125.6 (98.74)	157.6 (74.90)	119.0 (75.04)	150.7 (66.70)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-29.0 (6.93)	1.3 (9.49)	-31.9 (11.44)	5.7 (14.69)	-31.2 (6.54)	5.2 (8.63)
95% CI	[-42.78, -15.21]	[-17.57, 20.17]	[-54.75, -9.11]	[-23.63, 34.94]	[-44.16, -18.33]	[-11.88, 22.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-30.29		-37.59		-36.41	
95% CI	[-53.72, -6.86]		[-74.80, -0.38]		[-57.80, -15.02]	
p-value	0.0119		0.0478		0.0010	
Hedges' g	-0.63		-0.48		-0.55	
95% CI	[-1.08, -0.18]		[-0.95, -0.01]		[-0.87, -0.22]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-31.9 (6.02)	5.5 (7.94)	-32.2 (9.20)	-7.3 (11.70)	-32.5 (5.39)	0.2 (6.96)
95% CI	[-43.92, -19.95]	[-10.26, 21.33]	[-50.55, -13.80]	[-30.70, 16.01]	[-43.13, -21.81]	[-13.59, 13.94]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.47		-24.83		-32.65	
95% CI	[-57.35, -17.60]		[-54.56, 4.91]		[-50.06, -15.24]	
p-value	0.0003		0.1002		0.0003	
Hedges' g	-0.87		-0.41		-0.63	
95% CI	[-1.34, -0.41]		[-0.89, 0.08]		[-0.97, -0.30]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	144.3 (51.90)	146.2 (48.43)	139.3 (54.33)	142.9 (42.08)	141.7 (53.12)	144.6 (45.19)
Visit 13/ET						
n/N2	73/82	38/42	86/94	35/40	159/176	73/82
Mean (SD)	110.5 (59.30)	154.7 (71.13)	110.2 (75.72)	161.5 (68.42)	110.3 (68.46)	157.9 (69.44)
EAP						
n/N2	65/82	34/42	82/94	35/40	147/176	69/82
Mean (SD)	106.3 (52.88)	147.4 (70.76)	106.7 (61.50)	156.6 (57.48)	106.5 (57.66)	152.1 (64.06)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.2 (5.55)	12.5 (7.70)	-26.3 (4.89)	15.8 (7.67)	-31.1 (3.73)	14.8 (5.49)
95% CI	[-46.23, -24.21]	[-2.78, 27.75]	[-36.01, -16.64]	[0.65, 31.03]	[-38.40, -23.70]	[3.97, 25.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-47.71		-42.17		-45.84	
95% CI	[-66.54, -28.88]		[-60.20, -24.13]		[-58.92, -32.76]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.00		-0.94		-0.97	
95% CI	[-1.41, -0.59]		[-1.35, -0.53]		[-1.26, -0.68]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.1 (4.91)	8.3 (6.79)	-28.0 (4.11)	12.9 (6.30)	-32.1 (3.17)	10.6 (4.60)
95% CI	[-45.87, -26.37]	[-5.22, 21.76]	[-36.16, -19.88]	[0.38, 25.35]	[-38.33, -25.81]	[1.52, 19.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.39		-40.88		-42.67	
95% CI	[-61.04, -27.74]		[-55.81, -25.95]		[-53.69, -31.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.12		-1.08		-1.09	
95% CI	[-1.56, -0.68]		[-1.49, -0.66]		[-1.40, -0.79]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.1.1.1.s1
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.9476		0.0667		0.0853	
Vist 13/ET	0.3766		0.0816		0.0538	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
EAP:n/N1 (%)	16/59 (27.1)	2/30 (6.7)	15/50 (30.0)	5/32 (15.6)	31/109 (28.4)	7/62 (11.3)
RR [95%-CI]; p-value	4.07 [1.00, 16.54], 0.0499		1.92 [0.77, 4.77], 0.1599		2.52 [1.18, 5.38], 0.0170	
OR [95%-CI]; p-value	5.21 [1.11, 24.42], 0.0232		2.31 [0.75, 7.16], 0.1392		3.12 [1.28, 7.60], 0.0095	
RD [95%-CI]; p-value	0.20 [0.06, 0.35], 0.0055		0.14 [-0.04, 0.32], 0.1150		0.17 [0.06, 0.29], 0.0037	
Vist 13/ET:n/N1 (%)	22/59 (37.3)	4/30 (13.3)	20/50 (40.0)	6/32 (18.8)	42/109 (38.5)	10/62 (16.1)
RR [95%-CI]; p-value	2.80 [1.06, 7.38], 0.0378		2.13 [0.96, 4.73], 0.0625		2.39 [1.29, 4.42], 0.0055	
OR [95%-CI]; p-value	3.86 [1.19, 12.55], 0.0188		2.89 [1.01, 8.28], 0.0437		3.26 [1.50, 7.10], 0.0022	
RD [95%-CI]; p-value	0.24 [0.07, 0.41], 0.0067		0.21 [0.02, 0.40], 0.0298		0.22 [0.09, 0.35], 0.0007	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
EAP:n/N2 (%)	30/82 (36.6)	4/42 (9.5)	34/94 (36.2)	0/40 (0.0)	64/176 (36.4)	4/82 (4.9)
RR [95%-CI]; p-value	3.84 [1.45, 10.18], 0.0068		29.30 [1.84, 466.48], 0.0168		7.45 [2.81, 19.77], <0.0001	
OR [95%-CI]; p-value	5.48 [1.78, 16.87], 0.0014		45.33 [2.70, 761.03], <0.0001		11.14 [3.90, 31.86], <0.0001	
RD [95%-CI]; p-value	0.27 [0.13, 0.41], 0.0001		0.35 [0.25, 0.45], <0.0001		0.31 [0.23, 0.40], <0.0001	
Vist 13/ET:n/N2 (%)	32/82 (39.0)	3/42 (7.1)	41/94 (43.6)	2/40 (5.0)	73/176 (41.5)	5/82 (6.1)
RR [95%-CI]; p-value	5.46 [1.78, 16.80], 0.0031		8.72 [2.22, 34.34], 0.0019		6.80 [2.86, 16.19], <0.0001	
OR [95%-CI]; p-value	8.32 [2.37, 29.19], 0.0002		14.70 [3.35, 64.52], <0.0001		10.91 [4.21, 28.31], <0.0001	
RD [95%-CI]; p-value	0.32 [0.19, 0.45], <0.0001		0.39 [0.27, 0.51], <0.0001		0.35 [0.26, 0.44], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_1_1_1_m_pth30pct_age.sas using SAS 9.4

Table 12.2.1.1.2.s1
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.1703		0.1485		0.0457	
Vist 13/ET	0.5271		0.5159		0.3523	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
EAP:n/N1 (%)	38/59 (64.4)	10/30 (33.3)	32/50 (64.0)	11/32 (34.4)	70/109 (64.2)	21/62 (33.9)
RR [95%-CI]; p-value	1.93 [1.13, 3.32], 0.0169		1.86 [1.10, 3.14], 0.0196		1.90 [1.30, 2.76], 0.0008	
OR [95%-CI]; p-value	3.62 [1.43, 9.15], 0.0054		3.39 [1.34, 8.61], 0.0088		3.50 [1.82, 6.75], 0.0001	
RD [95%-CI]; p-value	0.31 [0.10, 0.52], 0.0035		0.30 [0.08, 0.51], 0.0061		0.30 [0.16, 0.45], <0.0001	
Vist 13/ET:n/N1 (%)	37/59 (62.7)	9/30 (30.0)	37/50 (74.0)	11/32 (34.4)	74/109 (67.9)	20/62 (32.3)
RR [95%-CI]; p-value	2.09 [1.17, 3.74], 0.0129		2.15 [1.30, 3.57], 0.0030		2.10 [1.43, 3.09], 0.0001	
OR [95%-CI]; p-value	3.92 [1.53, 10.07], 0.0035		5.43 [2.07, 14.26], 0.0004		4.44 [2.28, 8.65], <0.0001	
RD [95%-CI]; p-value	0.33 [0.12, 0.53], 0.0018		0.40 [0.19, 0.60], 0.0001		0.36 [0.21, 0.50], <0.0001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
EAP:n/N2 (%)	49/82 (59.8)	7/42 (16.7)	58/94 (61.7)	7/40 (17.5)	107/176 (60.8)	14/82 (17.1)
RR [95%-CI]; p-value	3.59 [1.78, 7.21], 0.0003		3.53 [1.77, 7.04], 0.0004		3.56 [2.18, 5.82], <0.0001	
OR [95%-CI]; p-value	7.42 [2.95, 18.70], <0.0001		7.60 [3.04, 18.97], <0.0001		7.53 [3.93, 14.43], <0.0001	
RD [95%-CI]; p-value	0.43 [0.28, 0.59], <0.0001		0.44 [0.29, 0.60], <0.0001		0.44 [0.33, 0.55], <0.0001	
Vist 13/ET:n/N2 (%)	53/82 (64.6)	10/42 (23.8)	59/94 (62.8)	9/40 (22.5)	112/176 (63.6)	19/82 (23.2)
RR [95%-CI]; p-value	2.71 [1.54, 4.77], 0.0005		2.79 [1.54, 5.06], 0.0007		2.75 [1.82, 4.14], <0.0001	
OR [95%-CI]; p-value	5.85 [2.52, 13.58], <0.0001		5.81 [2.48, 13.61], <0.0001		5.80 [3.19, 10.55], <0.0001	
RD [95%-CI]; p-value	0.41 [0.24, 0.57], <0.0001		0.40 [0.24, 0.56], <0.0001		0.40 [0.29, 0.52], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_1_1_2_m_pth10pct_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9627		0.4055		0.5571	
Comparison Baseline vs. EAP	0.0600		0.2124		0.0278	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	19.2 (4.94)	19.7 (6.19)	17.9 (5.41)	18.5 (6.16)	18.6 (5.18)	19.1 (6.15)
Visit 13/ET						
n/N1	57/59	30/30	46/50	28/32	103/109	58/62
Mean (SD)	64.4 (25.19)	16.6 (6.36)	60.7 (25.34)	18.8 (6.68)	62.7 (25.20)	17.7 (6.55)
EAP						
n/N1	52/59	30/30	42/50	26/32	94/109	56/62
Mean (SD)	65.6 (25.57)	17.1 (6.05)	60.0 (21.58)	18.6 (6.77)	63.1 (23.91)	17.8 (6.38)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.2 (2.73)	-2.9 (3.77)	42.8 (3.02)	0.4 (3.88)	43.9 (2.03)	-1.3 (2.70)
95% CI	[39.73, 50.60]	[-10.41, 4.59]	[36.73, 48.77]	[-7.29, 8.17]	[39.93, 47.96]	[-6.60, 4.05]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.08		42.31		45.22	
95% CI	[38.81, 57.34]		[32.50, 52.13]		[38.54, 51.90]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.32		2.06		2.22	
95% CI	[1.76, 2.88]		[1.49, 2.63]		[1.82, 2.62]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.7 (2.86)	-2.3 (3.78)	42.4 (2.68)	0.7 (3.41)	44.6 (1.99)	-0.9 (2.57)
95% CI	[41.04, 52.45]	[-9.84, 5.19]	[37.08, 47.78]	[-6.15, 7.45]	[40.63, 48.49]	[-5.94, 4.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.07		41.78		45.42	
95% CI	[39.62, 58.52]		[33.12, 50.44]		[39.00, 51.85]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.38		2.39		2.39	
95% CI	[1.80, 2.95]		[1.76, 3.02]		[1.96, 2.81]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	20.9 (5.09)	18.9 (4.88)	20.6 (5.43)	20.1 (4.90)	20.8 (5.26)	19.5 (4.89)
Visit 13/ET						
n/N2	74/82	38/42	86/94	34/40	160/176	72/82
Mean (SD)	65.6 (24.33)	18.2 (6.03)	68.4 (23.86)	20.8 (6.70)	67.1 (24.04)	19.4 (6.45)
EAP						
n/N2	66/82	34/42	82/94	35/40	148/176	69/82
Mean (SD)	68.2 (19.37)	18.1 (6.48)	70.2 (20.61)	20.1 (6.32)	69.3 (20.03)	19.1 (6.43)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.8 (2.27)	-0.6 (3.19)	47.7 (2.16)	0.0 (3.43)	46.3 (1.56)	-0.3 (2.33)
95% CI	[40.29, 49.29]	[-6.90, 5.72]	[43.43, 51.97]	[-6.78, 6.80]	[43.18, 49.34]	[-4.91, 4.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.38		47.69		46.59	
95% CI	[37.57, 53.18]		[39.67, 55.71]		[41.05, 52.12]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.34		2.38		2.38	
95% CI	[1.84, 2.83]		[1.88, 2.88]		[2.03, 2.73]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.3 (1.87)	-0.5 (2.62)	49.5 (1.87)	-0.2 (2.87)	48.4 (1.33)	-0.4 (1.95)
95% CI	[43.59, 51.01]	[-5.72, 4.67]	[45.74, 53.17]	[-5.88, 5.49]	[45.78, 51.04]	[-4.26, 3.42]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.83		49.65		48.83	
95% CI	[41.40, 54.25]		[42.86, 56.45]		[44.17, 53.50]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.17		2.92		3.05	
95% CI	[2.57, 3.78]		[2.38, 3.46]		[2.64, 3.45]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.1.1.s1
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4710		0.8918		0.4398	
Vist 13/ET	0.8689		0.5655		0.6865	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
EAP:n/N1 (%)	49/59 (83.1)	0/30 (0.0)	40/50 (80.0)	2/32 (6.3)	89/109 (81.7)	2/62 (3.2)
RR [95%-CI]; p-value	50.66 [3.23, 793.59], 0.0052		12.80 [3.32, 49.33], 0.0002		25.31 [6.46, 99.24], <0.0001	
OR [95%-CI]; p-value	294.00 [16.56, 5218.42], <0.0001		60.00 [12.23, 294.30], <0.0001		133.50 [30.09, 592.33], <0.0001	
RD [95%-CI]; p-value	0.81 [0.71, 0.92], <0.0001		0.74 [0.60, 0.88], <0.0001		0.78 [0.70, 0.87], <0.0001	
Vist 13/ET:n/N1 (%)	52/59 (88.1)	1/30 (3.3)	43/50 (86.0)	2/32 (6.3)	95/109 (87.2)	3/62 (4.8)
RR [95%-CI]; p-value	26.44 [3.84, 182.03], 0.0009		13.76 [3.58, 52.90], 0.0001		18.01 [5.96, 54.45], <0.0001	
OR [95%-CI]; p-value	215.43 [25.25, 1838.29], <0.0001		92.14 [17.89, 474.62], <0.0001		133.45 [36.79, 484.11], <0.0001	
RD [95%-CI]; p-value	0.85 [0.74, 0.95], <0.0001		0.80 [0.67, 0.93], <0.0001		0.82 [0.74, 0.91], <0.0001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
EAP:n/N2 (%)	64/82 (78.0)	2/42 (4.8)	80/94 (85.1)	3/40 (7.5)	144/176 (81.8)	5/82 (6.1)
RR [95%-CI]; p-value	16.39 [4.22, 63.69], <0.0001		11.35 [3.81, 33.80], <0.0001		13.42 [5.72, 31.46], <0.0001	
OR [95%-CI]; p-value	71.11 [15.66, 322.98], <0.0001		70.48 [19.08, 260.26], <0.0001		69.30 [25.95, 185.07], <0.0001	
RD [95%-CI]; p-value	0.73 [0.62, 0.84], <0.0001		0.78 [0.67, 0.88], <0.0001		0.76 [0.68, 0.83], <0.0001	
Vist 13/ET:n/N2 (%)	65/82 (79.3)	1/42 (2.4)	80/94 (85.1)	4/40 (10.0)	145/176 (82.4)	5/82 (6.1)
RR [95%-CI]; p-value	33.29 [4.79, 231.59], 0.0004		8.51 [3.35, 21.65], <0.0001		13.51 [5.76, 31.68], <0.0001	
OR [95%-CI]; p-value	156.76 [20.09, 1223.00], <0.0001		51.43 [15.82, 167.16], <0.0001		72.03 [26.92, 192.73], <0.0001	
RD [95%-CI]; p-value	0.77 [0.67, 0.87], <0.0001		0.75 [0.63, 0.87], <0.0001		0.76 [0.69, 0.84], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_1_1_m_25d30_age.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9342		0.1171		0.2033	
Comparison Baseline vs. EAP	0.3502		0.0506		0.0325	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	142.6 (52.18)	141.7 (50.75)	143.8 (65.03)	155.0 (69.63)	143.2 (58.75)	148.9 (61.65)
Visit 13/ET						
n/N1	64/71	32/33	65/71	32/39	129/142	64/72
Mean (SD)	108.7 (59.84)	142.6 (57.79)	99.4 (53.43)	167.4 (98.25)	104.0 (56.67)	155.0 (80.93)
EAP						
n/N1	60/71	31/33	61/71	32/39	121/142	63/72
Mean (SD)	104.6 (46.05)	147.6 (61.27)	103.5 (52.34)	159.2 (80.14)	104.0 (49.12)	153.5 (71.14)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-33.0 (5.34)	3.5 (7.55)	-41.6 (6.06)	10.8 (8.66)	-37.3 (4.03)	7.2 (5.72)
95% CI	[-43.59, -22.38]	[-11.52, 18.47]	[-53.68, -29.62]	[-6.39, 28.02]	[-45.28, -29.40]	[-4.10, 18.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-36.46		-52.46		-44.52	
95% CI	[-54.83, -18.09]		[-73.55, -31.38]		[-58.33, -30.71]	
p-value	0.0002		<0.0001		<0.0001	
Hedges' g	-0.84		-0.97		-0.91	
95% CI	[-1.28, -0.40]		[-1.41, -0.53]		[-1.23, -0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-37.8 (4.90)	8.5 (6.81)	-36.6 (4.92)	8.9 (6.81)	-37.3 (3.47)	9.0 (4.81)
95% CI	[-47.50, -28.04]	[-5.04, 22.04]	[-46.35, -26.80]	[-4.63, 22.41]	[-44.19, -30.48]	[-0.50, 18.50]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-46.27		-45.47		-46.33	
95% CI	[-62.95, -29.59]		[-62.19, -28.75]		[-58.05, -34.62]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.16		-1.07		-1.12	
95% CI	[-1.62, -0.69]		[-1.52, -0.62]		[-1.45, -0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	151.1 (59.70)	142.6 (42.48)	151.3 (63.64)	156.2 (55.43)	151.2 (61.53)	148.8 (48.96)
Visit 13/ET						
n/N2	65/70	36/39	67/73	31/33	132/143	67/72
Mean (SD)	119.6 (63.76)	154.0 (71.73)	132.4 (113.93)	172.5 (65.96)	126.1 (92.56)	162.6 (69.23)
EAP						
n/N2	57/70	33/39	63/73	29/33	120/143	62/72
Mean (SD)	114.8 (55.57)	144.7 (69.53)	122.4 (93.36)	154.6 (43.60)	118.8 (77.52)	149.3 (58.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-32.1 (6.89)	11.3 (9.27)	-16.2 (7.90)	13.7 (11.62)	-25.2 (5.41)	14.5 (7.62)
95% CI	[-45.77, -18.44]	[-7.14, 29.65]	[-31.85, -0.50]	[-9.37, 36.75]	[-35.87, -14.52]	[-0.54, 29.52]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.36		-29.86		-39.68	
95% CI	[-66.34, -20.37]		[-57.77, -1.95]		[-58.12, -21.25]	
p-value	0.0003		0.0363		<0.0001	
Hedges' g	-0.82		-0.48		-0.63	
95% CI	[-1.24, -0.40]		[-0.91, -0.05]		[-0.93, -0.33]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-31.2 (5.96)	6.6 (7.85)	-22.8 (6.62)	-0.2 (9.76)	-27.2 (4.47)	3.6 (6.23)
95% CI	[-43.01, -19.30]	[-9.01, 22.18]	[-35.95, -9.66]	[-19.61, 19.18]	[-36.03, -18.39]	[-8.67, 15.90]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.74		-22.59		-30.82	
95% CI	[-57.37, -18.10]		[-46.04, 0.87]		[-45.95, -15.70]	
p-value	0.0002		0.0589		<0.0001	
Hedges' g	-0.85		-0.44		-0.63	
95% CI	[-1.29, -0.41]		[-0.88, 0.00]		[-0.94, -0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.1.1.1.s2
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4291		0.4819		0.2839	
Vist 13/ET	0.8882		0.5404		0.6074	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
EAP:n/N1 (%)	25/71 (35.2)	2/33 (6.1)	25/71 (35.2)	2/39 (5.1)	50/142 (35.2)	4/72 (5.6)
RR [95%-CI]; p-value	5.81 [1.46, 23.09], 0.0124		6.87 [1.72, 27.46], 0.0065		6.34 [2.38, 16.86], 0.0002	
OR [95%-CI]; p-value	8.42 [1.86, 38.15], 0.0016		10.05 [2.23, 45.24], 0.0005		9.24 [3.18, 26.82], <0.0001	
RD [95%-CI]; p-value	0.29 [0.15, 0.43], <0.0001		0.30 [0.17, 0.43], <0.0001		0.30 [0.20, 0.39], <0.0001	
Vist 13/ET:n/N1 (%)	27/71 (38.0)	3/33 (9.1)	34/71 (47.9)	4/39 (10.3)	61/142 (43.0)	7/72 (9.7)
RR [95%-CI]; p-value	4.18 [1.37, 12.81], 0.0122		4.67 [1.79, 12.19], 0.0016		4.42 [2.13, 9.16], <0.0001	
OR [95%-CI]; p-value	6.14 [1.71, 22.07], 0.0024		8.04 [2.59, 25.00], <0.0001		6.99 [3.00, 16.32], <0.0001	
RD [95%-CI]; p-value	0.29 [0.14, 0.44], 0.0001		0.38 [0.23, 0.53], <0.0001		0.33 [0.23, 0.44], <0.0001	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
EAP:n/N2 (%)	21/70 (30.0)	4/39 (10.3)	24/73 (32.9)	3/33 (9.1)	45/143 (31.5)	7/72 (9.7)
RR [95%-CI]; p-value	2.93 [1.08, 7.91], 0.0345		3.62 [1.17, 11.17], 0.0255		3.24 [1.54, 6.81], 0.0020	
OR [95%-CI]; p-value	3.75 [1.18, 11.89], 0.0188		4.90 [1.36, 17.68], 0.0093		4.26 [1.81, 10.03], 0.0004	
RD [95%-CI]; p-value	0.20 [0.05, 0.34], 0.0070		0.24 [0.09, 0.38], 0.0014		0.22 [0.12, 0.32], <0.0001	
Vist 13/ET:n/N2 (%)	27/70 (38.6)	4/39 (10.3)	27/73 (37.0)	4/33 (12.1)	54/143 (37.8)	8/72 (11.1)
RR [95%-CI]; p-value	3.76 [1.42, 9.96], 0.0077		3.05 [1.16, 8.02], 0.0236		3.40 [1.71, 6.75], 0.0005	
OR [95%-CI]; p-value	5.49 [1.76, 17.20], 0.0017		4.26 [1.35, 13.42], 0.0092		4.85 [2.16, 10.90], <0.0001	
RD [95%-CI]; p-value	0.28 [0.13, 0.43], 0.0002		0.25 [0.09, 0.41], 0.0019		0.27 [0.16, 0.37], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_1_1_1_m_pth30pct_sex.sas using SAS 9.4

Table 12.2.1.1.2.s2
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4569		0.4860		0.9870	
Vist 13/ET	0.4441		0.4840		0.9504	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
EAP:n/N1 (%)	47/71 (66.2)	7/33 (21.2)	49/71 (69.0)	12/39 (30.8)	96/142 (67.6)	19/72 (26.4)
RR [95%-CI]; p-value	3.12 [1.58, 6.15], 0.0010		2.24 [1.37, 3.68], 0.0014		2.56 [1.71, 3.83], <0.0001	
OR [95%-CI]; p-value	7.27 [2.76, 19.16], <0.0001		5.01 [2.15, 11.68], 0.0001		5.82 [3.10, 10.94], <0.0001	
RD [95%-CI]; p-value	0.45 [0.27, 0.63], <0.0001		0.38 [0.20, 0.56], <0.0001		0.41 [0.28, 0.54], <0.0001	
Vist 13/ET:n/N1 (%)	49/71 (69.0)	11/33 (33.3)	50/71 (70.4)	10/39 (25.6)	99/142 (69.7)	21/72 (29.2)
RR [95%-CI]; p-value	2.07 [1.25, 3.44], 0.0049		2.75 [1.58, 4.79], 0.0004		2.39 [1.64, 3.48], <0.0001	
OR [95%-CI]; p-value	4.45 [1.85, 10.75], 0.0006		6.90 [2.86, 16.67], <0.0001		5.59 [3.00, 10.41], <0.0001	
RD [95%-CI]; p-value	0.36 [0.16, 0.55], 0.0003		0.45 [0.27, 0.62], <0.0001		0.41 [0.28, 0.53], <0.0001	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
EAP:n/N2 (%)	40/70 (57.1)	10/39 (25.6)	41/73 (56.2)	6/33 (18.2)	81/143 (56.6)	16/72 (22.2)
RR [95%-CI]; p-value	2.23 [1.26, 3.95], 0.0060		3.09 [1.46, 6.55], 0.0033		2.55 [1.62, 4.02], <0.0001	
OR [95%-CI]; p-value	3.87 [1.64, 9.14], 0.0016		5.77 [2.13, 15.64], 0.0003		4.57 [2.40, 8.73], <0.0001	
RD [95%-CI]; p-value	0.32 [0.14, 0.49], 0.0006		0.38 [0.21, 0.55], <0.0001		0.34 [0.22, 0.47], <0.0001	
Vist 13/ET:n/N2 (%)	41/70 (58.6)	8/39 (20.5)	46/73 (63.0)	10/33 (30.3)	87/143 (60.8)	18/72 (25.0)
RR [95%-CI]; p-value	2.86 [1.49, 5.46], 0.0015		2.08 [1.20, 3.59], 0.0086		2.43 [1.60, 3.71], <0.0001	
OR [95%-CI]; p-value	5.48 [2.20, 13.63], 0.0001		3.92 [1.62, 9.46], 0.0018		4.66 [2.48, 8.75], <0.0001	
RD [95%-CI]; p-value	0.38 [0.21, 0.55], <0.0001		0.33 [0.14, 0.52], 0.0008		0.36 [0.23, 0.49], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_1_1_2_m_pth10pct_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0439		0.4164		0.0455	
Comparison Baseline vs. EAP	0.1869		0.2142		0.0706	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	20.3 (5.11)	20.0 (5.13)	19.6 (5.06)	18.6 (4.99)	20.0 (5.08)	19.2 (5.08)
Visit 13/ET						
n/N1	66/71	32/33	65/71	31/39	131/142	63/72
Mean (SD)	72.6 (23.42)	18.2 (6.56)	69.1 (24.27)	18.1 (6.08)	70.8 (23.82)	18.1 (6.28)
EAP						
n/N1	61/71	31/33	61/71	32/39	122/142	63/72
Mean (SD)	73.2 (22.17)	18.3 (6.50)	69.4 (20.80)	18.0 (6.12)	71.3 (21.49)	18.1 (6.26)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	52.6 (2.36)	-1.9 (3.39)	49.5 (2.52)	-1.1 (3.66)	51.0 (1.72)	-1.4 (2.49)
95% CI	[47.88, 57.25]	[-8.63, 4.82]	[44.49, 54.52]	[-8.36, 6.18]	[47.59, 54.39]	[-6.31, 3.50]
Diff in LS-Mean [ER-Calcifediol - Placebo]	54.46		50.59		52.39	
95% CI	[46.27, 62.66]		[41.75, 59.44]		[46.42, 58.37]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.84		2.43		2.64	
95% CI	[2.26, 3.41]		[1.88, 2.97]		[2.24, 3.04]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	53.7 (2.26)	-1.7 (3.17)	49.9 (2.16)	-0.7 (2.98)	51.8 (1.56)	-1.1 (2.17)
95% CI	[49.16, 58.15]	[-7.99, 4.62]	[45.66, 54.22]	[-6.58, 5.26]	[48.69, 54.84]	[-5.39, 3.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	55.34		50.60		52.88	
95% CI	[47.60, 63.09]		[43.28, 57.92]		[47.60, 58.15]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.12		2.99		3.07	
95% CI	[2.50, 3.74]		[2.38, 3.59]		[2.64, 3.51]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	20.1 (5.08)	18.6 (5.66)	19.7 (6.04)	20.3 (6.00)	19.9 (5.57)	19.4 (5.84)
Visit 13/ET						
n/N2	65/70	36/39	67/73	31/33	132/143	67/72
Mean (SD)	57.5 (23.62)	16.9 (5.86)	62.4 (24.60)	21.6 (6.95)	60.0 (24.15)	19.1 (6.76)
EAP						
n/N2	57/70	33/39	63/73	29/33	120/143	62/72
Mean (SD)	60.4 (20.52)	17.1 (6.05)	64.2 (21.85)	21.0 (6.65)	62.4 (21.22)	18.9 (6.60)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	37.5 (2.35)	-1.8 (3.17)	42.9 (2.43)	0.7 (3.57)	40.1 (1.68)	-0.4 (2.37)
95% CI	[32.79, 42.12]	[-8.06, 4.52]	[38.11, 47.74]	[-6.39, 7.80]	[36.80, 43.43]	[-5.07, 4.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	39.22		42.22		40.52	
95% CI	[31.35, 47.09]		[33.62, 50.81]		[34.79, 46.24]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.05		2.12		2.10	
95% CI	[1.56, 2.55]		[1.60, 2.63]		[1.74, 2.45]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	40.4 (2.17)	-1.8 (2.85)	44.4 (2.22)	0.8 (3.28)	42.4 (1.55)	-0.4 (2.16)
95% CI	[36.10, 44.71]	[-7.46, 3.89]	[40.00, 48.83]	[-5.68, 7.34]	[39.31, 45.43]	[-4.67, 3.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.20		43.59		42.78	
95% CI	[35.04, 49.35]		[35.72, 51.46]		[37.54, 48.03]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.55		2.46		2.53	
95% CI	[1.99, 3.12]		[1.90, 3.03]		[2.12, 2.93]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.1.1.s2
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3294		0.1489		0.6681	
Vist 13/ET	0.3396		0.0894		0.4257	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
EAP:n/N1 (%)	58/71 (81.7)	2/33 (6.1)	60/71 (84.5)	1/39 (2.6)	118/142 (83.1)	3/72 (4.2)
RR [95%-CI]; p-value	13.48 [3.50, 51.88], 0.0002		32.96 [4.75, 228.71], 0.0004		19.94 [6.57, 60.53], <0.0001	
OR [95%-CI]; p-value	69.15 [14.66, 326.22], <0.0001		207.27 [25.71, 1670.85], <0.0001		113.08 [32.84, 389.38], <0.0001	
RD [95%-CI]; p-value	0.76 [0.63, 0.88], <0.0001		0.82 [0.72, 0.92], <0.0001		0.79 [0.71, 0.87], <0.0001	
Vist 13/ET:n/N1 (%)	61/71 (85.9)	2/33 (6.1)	62/71 (87.3)	1/39 (2.6)	123/142 (86.6)	3/72 (4.2)
RR [95%-CI]; p-value	14.18 [3.69, 54.49], 0.0001		34.06 [4.91, 236.21], 0.0004		20.79 [6.85, 63.06], <0.0001	
OR [95%-CI]; p-value	94.55 [19.50, 458.36], <0.0001		261.78 [31.89, 2148.60], <0.0001		148.89 [42.54, 521.16], <0.0001	
RD [95%-CI]; p-value	0.80 [0.68, 0.91], <0.0001		0.85 [0.76, 0.94], <0.0001		0.82 [0.75, 0.90], <0.0001	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
EAP:n/N2 (%)	55/70 (78.6)	0/39 (0.0)	60/73 (82.2)	4/33 (12.1)	115/143 (80.4)	4/72 (5.6)
RR [95%-CI]; p-value	62.07 [3.94, 977.71], 0.0033		6.78 [2.69, 17.10], <0.0001		14.48 [5.57, 37.65], <0.0001	
OR [95%-CI]; p-value	286.00 [16.59, 4931.18], <0.0001		33.46 [10.03, 111.67], <0.0001		69.82 [23.48, 207.61], <0.0001	
RD [95%-CI]; p-value	0.77 [0.67, 0.88], <0.0001		0.70 [0.56, 0.84], <0.0001		0.75 [0.66, 0.83], <0.0001	
Vist 13/ET:n/N2 (%)	56/70 (80.0)	0/39 (0.0)	61/73 (83.6)	5/33 (15.2)	117/143 (81.8)	5/72 (6.9)
RR [95%-CI]; p-value	63.20 [4.01, 995.26], 0.0032		5.52 [2.44, 12.44], <0.0001		11.78 [5.04, 27.54], <0.0001	
OR [95%-CI]; p-value	312.00 [18.04, 5395.59], <0.0001		28.47 [9.15, 88.58], <0.0001		60.30 [22.11, 164.42], <0.0001	
RD [95%-CI]; p-value	0.79 [0.69, 0.89], <0.0001		0.68 [0.54, 0.83], <0.0001		0.75 [0.66, 0.84], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_1_1_m_25d30_sex.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5995		0.4874		0.4043	
Comparison Baseline vs. EAP	0.1686		0.0534		0.0148	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	147.0 (59.64)	140.1 (45.67)	150.3 (69.42)	171.5 (79.25)	148.7 (64.65)	154.1 (64.32)
Visit 13/ET						
n/N1	66/73	33/36	71/77	26/29	137/150	59/65
Mean (SD)	111.6 (64.45)	140.2 (48.90)	119.0 (93.91)	186.0 (89.16)	115.5 (80.86)	160.4 (72.62)
EAP						
n/N1	60/73	31/36	64/77	25/29	124/150	56/65
Mean (SD)	105.1 (48.83)	137.1 (52.48)	112.3 (72.47)	174.2 (85.50)	108.8 (62.02)	153.7 (70.98)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.2 (5.66)	4.3 (8.02)	-32.6 (6.82)	12.8 (11.32)	-34.7 (4.48)	10.3 (6.87)
95% CI	[-46.45, -24.00]	[-11.59, 20.26]	[-46.19, -19.11]	[-9.68, 35.26]	[-43.51, -25.84]	[-3.28, 23.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-39.56		-45.44		-44.95	
95% CI	[-59.12, -20.00]		[-71.76, -19.11]		[-61.13, -28.76]	
p-value	0.0001		0.0009		<0.0001	
Hedges' g	-0.91		-0.78		-0.84	
95% CI	[-1.34, -0.47]		[-1.24, -0.32]		[-1.15, -0.52]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-38.6 (4.76)	5.5 (6.65)	-36.9 (4.83)	8.1 (7.75)	-38.2 (3.40)	7.8 (5.08)
95% CI	[-48.04, -29.14]	[-7.69, 18.72]	[-46.46, -27.25]	[-7.30, 23.53]	[-44.87, -31.46]	[-2.24, 17.82]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.11		-44.97		-45.96	
95% CI	[-60.45, -27.77]		[-63.18, -26.76]		[-58.02, -33.90]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.25		-1.08		-1.17	
95% CI	[-1.71, -0.78]		[-1.57, -0.60]		[-1.51, -0.84]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	146.6 (52.26)	144.3 (47.10)	144.5 (58.02)	144.8 (47.39)	145.6 (55.00)	144.6 (46.95)
Visit 13/ET						
n/N2	63/68	35/36	61/67	37/43	124/135	72/79
Mean (SD)	116.9 (59.40)	156.7 (77.59)	112.9 (87.26)	158.6 (78.16)	114.9 (74.14)	157.7 (77.34)
EAP						
n/N2	57/68	33/36	60/67	36/43	117/135	69/79
Mean (SD)	114.3 (53.11)	154.6 (74.99)	114.0 (80.78)	145.1 (42.98)	114.1 (68.42)	149.6 (60.17)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-29.7 (6.71)	10.7 (9.00)	-22.9 (7.86)	9.8 (10.10)	-26.8 (5.23)	11.1 (6.86)
95% CI	[-43.07, -16.42]	[-7.17, 28.57]	[-38.53, -7.33]	[-10.22, 29.90]	[-37.14, -16.51]	[-2.46, 24.62]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.44		-32.78		-37.90	
95% CI	[-62.74, -18.15]		[-58.26, -7.29]		[-54.93, -20.87]	
p-value	0.0005		0.0123		<0.0001	
Hedges' g	-0.74		-0.56		-0.65	
95% CI	[-1.17, -0.32]		[-0.97, -0.15]		[-0.95, -0.36]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.6 (6.12)	8.2 (8.05)	-21.6 (6.78)	1.8 (8.76)	-25.7 (4.59)	5.2 (5.99)
95% CI	[-41.79, -17.46]	[-7.75, 24.24]	[-35.09, -8.16]	[-15.63, 19.18]	[-34.79, -16.67]	[-6.62, 17.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.87		-23.40		-30.92	
95% CI	[-57.97, -17.77]		[-45.44, -1.36]		[-45.82, -16.02]	
p-value	0.0003		0.0377		<0.0001	
Hedges' g	-0.80		-0.45		-0.61	
95% CI	[-1.24, -0.36]		[-0.87, -0.04]		[-0.91, -0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.1.1.1.s3
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2214		0.9324		0.3574	
Vist 13/ET	0.2317		0.7714		0.2801	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
EAP:n/N1 (%)	28/73 (38.4)	2/36 (5.6)	27/77 (35.1)	2/29 (6.9)	55/150 (36.7)	4/65 (6.2)
RR [95%-CI]; p-value	6.90 [1.74, 27.39], 0.0060		5.08 [1.29, 20.04], 0.0201		5.96 [2.25, 15.76], 0.0003	
OR [95%-CI]; p-value	10.58 [2.36, 47.51], 0.0003		7.29 [1.61, 33.02], 0.0037		8.83 [3.04, 25.60], <0.0001	
RD [95%-CI]; p-value	0.33 [0.19, 0.46], <0.0001		0.28 [0.14, 0.42], <0.0001		0.31 [0.21, 0.40], <0.0001	
Vist 13/ET:n/N1 (%)	29/73 (39.7)	2/36 (5.6)	34/77 (44.2)	3/29 (10.3)	63/150 (42.0)	5/65 (7.7)
RR [95%-CI]; p-value	7.15 [1.81, 28.31], 0.0051		4.27 [1.42, 12.83], 0.0097		5.46 [2.30, 12.94], 0.0001	
OR [95%-CI]; p-value	11.20 [2.50, 50.27], 0.0002		6.85 [1.91, 24.57], 0.0011		8.69 [3.30, 22.88], <0.0001	
RD [95%-CI]; p-value	0.34 [0.21, 0.48], <0.0001		0.34 [0.18, 0.49], <0.0001		0.34 [0.24, 0.45], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
EAP:n/N2 (%)	18/68 (26.5)	4/36 (11.1)	22/67 (32.8)	3/43 (7.0)	40/135 (29.6)	7/79 (8.9)
RR [95%-CI]; p-value	2.38 [0.87, 6.51], 0.0906		4.71 [1.50, 14.77], 0.0080		3.34 [1.57, 7.10], 0.0017	
OR [95%-CI]; p-value	2.88 [0.89, 9.29], 0.0681		6.52 [1.81, 23.43], 0.0016		4.33 [1.83, 10.23], 0.0004	
RD [95%-CI]; p-value	0.15 [0.01, 0.30], 0.0402		0.26 [0.12, 0.39], 0.0002		0.21 [0.11, 0.31], <0.0001	
Vist 13/ET:n/N2 (%)	25/68 (36.8)	5/36 (13.9)	27/67 (40.3)	5/43 (11.6)	52/135 (38.5)	10/79 (12.7)
RR [95%-CI]; p-value	2.65 [1.11, 6.33], 0.0285		3.47 [1.45, 8.31], 0.0053		3.04 [1.64, 5.64], 0.0004	
OR [95%-CI]; p-value	3.60 [1.24, 10.46], 0.0143		5.13 [1.79, 14.70], 0.0012		4.32 [2.05, 9.14], <0.0001	
RD [95%-CI]; p-value	0.23 [0.07, 0.39], 0.0053		0.29 [0.14, 0.44], 0.0002		0.26 [0.15, 0.37], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_1_1_1_m_pth30pct_wt.sas using SAS 9.4

Table 12.2.1.1.2.s3
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.7162		0.8248		0.6665	
Vist 13/ET	0.9178		0.6146		0.7647	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
EAP:n/N1 (%)	46/73 (63.0)	8/36 (22.2)	49/77 (63.6)	7/29 (24.1)	95/150 (63.3)	15/65 (23.1)
RR [95%-CI]; p-value	2.84 [1.50, 5.36], 0.0013		2.64 [1.35, 5.14], 0.0044		2.74 [1.73, 4.35], <0.0001	
OR [95%-CI]; p-value	5.96 [2.38, 14.94], <0.0001		5.50 [2.09, 14.49], 0.0003		5.76 [2.96, 11.20], <0.0001	
RD [95%-CI]; p-value	0.41 [0.23, 0.58], <0.0001		0.39 [0.21, 0.58], <0.0001		0.40 [0.27, 0.53], <0.0001	
Vist 13/ET:n/N1 (%)	48/73 (65.8)	10/36 (27.8)	51/77 (66.2)	7/29 (24.1)	99/150 (66.0)	17/65 (26.2)
RR [95%-CI]; p-value	2.37 [1.36, 4.11], 0.0022		2.74 [1.41, 5.33], 0.0029		2.52 [1.65, 3.86], <0.0001	
OR [95%-CI]; p-value	4.99 [2.08, 11.97], 0.0002		6.16 [2.33, 16.31], 0.0001		5.48 [2.87, 10.48], <0.0001	
RD [95%-CI]; p-value	0.38 [0.20, 0.56], <0.0001		0.42 [0.23, 0.61], <0.0001		0.40 [0.27, 0.53], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
EAP:n/N2 (%)	41/68 (60.3)	9/36 (25.0)	41/67 (61.2)	11/43 (25.6)	82/135 (60.7)	20/79 (25.3)
RR [95%-CI]; p-value	2.41 [1.33, 4.38], 0.0039		2.39 [1.39, 4.12], 0.0017		2.40 [1.60, 3.59], <0.0001	
OR [95%-CI]; p-value	4.56 [1.86, 11.17], 0.0006		4.59 [1.97, 10.66], 0.0003		4.56 [2.47, 8.43], <0.0001	
RD [95%-CI]; p-value	0.35 [0.17, 0.54], 0.0002		0.36 [0.18, 0.53], <0.0001		0.35 [0.23, 0.48], <0.0001	
Vist 13/ET:n/N2 (%)	42/68 (61.8)	9/36 (25.0)	45/67 (67.2)	13/43 (30.2)	87/135 (64.4)	22/79 (27.8)
RR [95%-CI]; p-value	2.47 [1.36, 4.48], 0.0029		2.22 [1.37, 3.60], 0.0012		2.31 [1.59, 3.37], <0.0001	
OR [95%-CI]; p-value	4.85 [1.97, 11.91], 0.0004		4.72 [2.06, 10.79], 0.0002		4.70 [2.56, 8.60], <0.0001	
RD [95%-CI]; p-value	0.37 [0.19, 0.55], <0.0001		0.37 [0.19, 0.55], <0.0001		0.37 [0.24, 0.49], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_1_1_2_m_pth10pct_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2314		0.4087		0.7792	
Comparison Baseline vs. EAP	0.8262		0.4435		0.5014	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	20.2 (5.14)	20.3 (5.36)	20.4 (5.79)	19.6 (6.37)	20.3 (5.47)	20.0 (5.80)
Visit 13/ET						
n/N1	67/73	33/36	71/77	25/29	138/150	58/65
Mean (SD)	69.2 (24.13)	18.3 (5.75)	68.4 (26.09)	20.8 (6.84)	68.8 (25.07)	19.4 (6.32)
EAP						
n/N1	60/73	31/36	64/77	25/29	124/150	56/65
Mean (SD)	72.3 (24.21)	18.7 (6.11)	70.8 (22.70)	20.6 (7.28)	71.5 (23.36)	19.5 (6.66)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.2 (2.41)	-2.1 (3.44)	48.2 (2.65)	0.8 (4.46)	48.7 (1.79)	-0.6 (2.78)
95% CI	[44.39, 53.97]	[-8.88, 4.77]	[42.93, 53.44]	[-8.08, 9.64]	[45.16, 52.21]	[-6.14, 4.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.23		47.41		49.33	
95% CI	[42.89, 59.57]		[37.10, 57.71]		[42.81, 55.86]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.59		2.12		2.36	
95% CI	[2.04, 3.13]		[1.57, 2.66]		[1.98, 2.75]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	52.5 (2.52)	-2.1 (3.52)	50.4 (2.39)	0.9 (3.82)	51.4 (1.73)	-0.6 (2.59)
95% CI	[47.47, 57.51]	[-9.06, 4.91]	[45.62, 55.11]	[-6.68, 8.51]	[48.01, 54.84]	[-5.67, 4.54]
Diff in LS-Mean [ER-Calcifediol - Placebo]	54.56		49.45		51.99	
95% CI	[45.94, 63.18]		[40.49, 58.41]		[45.85, 58.13]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.79		2.58		2.71	
95% CI	[2.20, 3.38]		[1.98, 3.17]		[2.29, 3.13]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	20.3 (5.05)	18.2 (5.37)	18.8 (5.20)	19.2 (4.93)	19.5 (5.16)	18.7 (5.13)
Visit 13/ET						
n/N2	64/68	35/36	61/67	37/43	125/135	72/79
Mean (SD)	60.8 (24.57)	16.8 (6.57)	62.6 (22.48)	19.2 (6.65)	61.7 (23.50)	18.1 (6.68)
EAP						
n/N2	58/68	33/36	60/67	36/43	118/135	69/79
Mean (SD)	61.6 (18.74)	16.7 (6.33)	62.5 (19.23)	18.7 (5.89)	62.1 (18.91)	17.7 (6.14)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	40.7 (2.47)	-1.4 (3.36)	43.5 (2.30)	-0.3 (2.96)	42.1 (1.68)	-1.0 (2.22)
95% CI	[35.76, 45.57]	[-8.11, 5.22]	[38.92, 48.07]	[-6.21, 5.54]	[38.82, 45.46]	[-5.37, 3.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.11		43.83		43.14	
95% CI	[33.77, 50.45]		[36.38, 51.28]		[37.64, 48.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.13		2.44		2.29	
95% CI	[1.63, 2.64]		[1.91, 2.97]		[1.92, 2.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	41.8 (1.96)	-1.3 (2.61)	43.6 (1.95)	-0.5 (2.52)	42.7 (1.38)	-0.9 (1.80)
95% CI	[37.87, 45.65]	[-6.46, 3.91]	[39.75, 47.51]	[-5.48, 4.54]	[40.00, 45.43]	[-4.47, 2.65]
Diff in LS-Mean [ER-Calcifediol - Placebo]	43.04		44.10		43.62	
95% CI	[36.50, 49.58]		[37.76, 50.44]		[39.14, 48.11]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.88		2.90		2.92	
95% CI	[2.29, 3.48]		[2.32, 3.48]		[2.50, 3.33]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.1.1.s3
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.9292		0.0848		0.1359	
Vist 13/ET	0.3761		0.5927		0.3183	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
EAP:n/N1 (%)	55/73 (75.3)	1/36 (2.8)	61/77 (79.2)	4/29 (13.8)	116/150 (77.3)	5/65 (7.7)
RR [95%-CI]; p-value	27.12 [3.91, 188.18], 0.0008		5.74 [2.30, 14.37], 0.0002		10.05 [4.31, 23.44], <0.0001	
OR [95%-CI]; p-value	106.94 [13.66, 837.23], <0.0001		23.83 [7.25, 78.36], <0.0001		40.94 [15.23, 110.09], <0.0001	
RD [95%-CI]; p-value	0.73 [0.61, 0.84], <0.0001		0.65 [0.50, 0.81], <0.0001		0.70 [0.60, 0.79], <0.0001	
Vist 13/ET:n/N1 (%)	61/73 (83.6)	2/36 (5.6)	65/77 (84.4)	3/29 (10.3)	126/150 (84.0)	5/65 (7.7)
RR [95%-CI]; p-value	15.04 [3.90, 58.06], <0.0001		8.16 [2.78, 23.93], 0.0001		10.92 [4.69, 25.42], <0.0001	
OR [95%-CI]; p-value	86.42 [18.26, 409.03], <0.0001		46.94 [12.24, 180.08], <0.0001		63.00 [22.91, 173.21], <0.0001	
RD [95%-CI]; p-value	0.78 [0.67, 0.89], <0.0001		0.74 [0.60, 0.88], <0.0001		0.76 [0.68, 0.85], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
EAP:n/N2 (%)	58/68 (85.3)	1/36 (2.8)	59/67 (88.1)	1/43 (2.3)	117/135 (86.7)	2/79 (2.5)
RR [95%-CI]; p-value	30.71 [4.43, 212.62], 0.0005		37.87 [5.45, 263.25], 0.0002		34.23 [8.70, 134.70], <0.0001	
OR [95%-CI]; p-value	203.00 [24.91, 1654.42], <0.0001		309.75 [37.32, 2570.73], <0.0001		250.25 [56.46, 1109.18], <0.0001	
RD [95%-CI]; p-value	0.83 [0.73, 0.93], <0.0001		0.86 [0.77, 0.95], <0.0001		0.84 [0.77, 0.91], <0.0001	
Vist 13/ET:n/N2 (%)	56/68 (82.4)	0/36 (0.0)	58/67 (86.6)	3/43 (7.0)	114/135 (84.4)	3/79 (3.8)
RR [95%-CI]; p-value	60.12 [3.82, 945.07], 0.0036		12.41 [4.15, 37.11], <0.0001		22.24 [7.31, 67.63], <0.0001	
OR [95%-CI]; p-value	336.00 [19.25, 5865.78], <0.0001		85.93 [21.89, 337.25], <0.0001		137.52 [39.64, 477.16], <0.0001	
RD [95%-CI]; p-value	0.81 [0.71, 0.91], <0.0001		0.80 [0.68, 0.91], <0.0001		0.81 [0.73, 0.88], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_1_1_m_25d30_wt.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6281		0.3976		0.4270	
Comparison Baseline vs. EAP	0.5565		0.4896		0.8714	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	144.8 (56.27)	139.1 (47.48)	142.4 (55.45)	142.2 (39.00)	143.5 (55.69)	140.6 (43.33)
Visit 13/ET						
n/N1	77/85	45/48	91/98	40/46	168/183	85/94
Mean (SD)	109.1 (59.00)	145.0 (57.89)	107.8 (84.29)	155.5 (64.34)	108.4 (73.58)	149.9 (60.87)
EAP						
n/N1	67/85	42/48	87/98	39/46	154/183	81/94
Mean (SD)	102.2 (48.51)	133.1 (49.75)	105.4 (73.69)	148.2 (45.88)	104.0 (63.80)	140.4 (48.22)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.2 (5.29)	6.4 (6.93)	-33.7 (6.47)	13.1 (9.75)	-34.7 (4.28)	10.1 (6.00)
95% CI	[-45.69, -24.73]	[-7.35, 20.10]	[-46.46, -20.87]	[-6.21, 32.38]	[-43.09, -26.25]	[-1.68, 21.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-41.58		-46.75		-44.81	
95% CI	[-58.88, -24.29]		[-69.90, -23.59]		[-59.33, -30.29]	
p-value	<0.0001		0.0001		<0.0001	
Hedges' g	-0.89		-0.76		-0.81	
95% CI	[-1.27, -0.51]		[-1.14, -0.37]		[-1.08, -0.54]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.9 (4.54)	0.3 (5.74)	-33.1 (5.19)	5.0 (7.75)	-34.2 (3.54)	2.9 (4.85)
95% CI	[-43.94, -25.94]	[-11.03, 11.72]	[-43.39, -22.84]	[-10.31, 20.39]	[-41.19, -27.23]	[-6.61, 12.49]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.28		-38.15		-37.16	
95% CI	[-49.80, -20.76]		[-56.63, -19.68]		[-48.99, -25.33]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.95		-0.77		-0.84	
95% CI	[-1.35, -0.54]		[-1.16, -0.38]		[-1.12, -0.56]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	150.0 (55.96)	148.4 (43.57)	158.7 (79.32)	179.1 (87.52)	153.9 (67.29)	164.4 (70.99)
Visit 13/ET						
n/N2	52/56	23/24	41/46	23/26	93/102	46/50
Mean (SD)	121.8 (65.68)	155.8 (78.81)	134.8 (101.91)	195.0 (105.73)	127.5 (83.36)	175.4 (94.31)
EAP						
n/N2	50/56	22/24	37/46	22/26	87/102	44/50
Mean (SD)	119.4 (52.95)	170.9 (83.20)	131.1 (80.24)	172.7 (88.43)	124.4 (65.78)	171.8 (84.86)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-28.9 (7.52)	10.6 (11.31)	-15.6 (8.47)	7.0 (11.37)	-23.0 (5.70)	10.2 (8.06)
95% CI	[-43.83, -13.87]	[-11.94, 33.14]	[-32.57, 1.30]	[-15.76, 29.73]	[-34.24, -11.71]	[-5.77, 26.09]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-39.45		-22.62		-33.13	
95% CI	[-66.53, -12.37]		[-51.25, 6.01]		[-52.69, -13.58]	
p-value	0.0049		0.1194		0.0010	
Hedges' g	-0.74		-0.48		-0.63	
95% CI	[-1.24, -0.24]		[-0.99, 0.03]		[-0.99, -0.27]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-33.9 (6.67)	20.9 (10.05)	-20.9 (6.99)	3.1 (9.08)	-27.6 (4.90)	12.5 (6.81)
95% CI	[-47.19, -20.59]	[0.86, 40.97]	[-34.91, -6.91]	[-15.08, 21.30]	[-37.32, -17.93]	[-0.96, 26.00]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-54.80		-24.02		-40.14	
95% CI	[-78.87, -30.73]		[-47.05, -0.99]		[-56.76, -23.53]	
p-value	<0.0001		0.0412		<0.0001	
Hedges' g	-1.15		-0.54		-0.88	
95% CI	[-1.68, -0.61]		[-1.07, -0.01]		[-1.25, -0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.1.1.1.s4
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2890		0.0677		0.6790	
Vist 13/ET	0.2563		0.8817		0.4242	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
EAP:n/N1 (%)	25/85 (29.4)	5/48 (10.4)	40/98 (40.8)	2/46 (4.3)	65/183 (35.5)	7/94 (7.4)
RR [95%-CI]; p-value	2.82 [1.16, 6.89], 0.0227		9.39 [2.37, 37.18], 0.0014		4.77 [2.28, 9.99], <0.0001	
OR [95%-CI]; p-value	3.58 [1.27, 10.11], 0.0118		15.17 [3.48, 66.20], <0.0001		6.85 [2.99, 15.66], <0.0001	
RD [95%-CI]; p-value	0.19 [0.06, 0.32], 0.0041		0.36 [0.25, 0.48], <0.0001		0.28 [0.19, 0.37], <0.0001	
Vist 13/ET:n/N1 (%)	31/85 (36.5)	6/48 (12.5)	49/98 (50.0)	6/46 (13.0)	80/183 (43.7)	12/94 (12.8)
RR [95%-CI]; p-value	2.92 [1.31, 6.49], 0.0087		3.83 [1.77, 8.30], 0.0006		3.42 [1.97, 5.96], <0.0001	
OR [95%-CI]; p-value	4.02 [1.53, 10.52], 0.0030		6.67 [2.59, 17.15], <0.0001		5.31 [2.71, 10.40], <0.0001	
RD [95%-CI]; p-value	0.24 [0.10, 0.38], 0.0007		0.37 [0.23, 0.51], <0.0001		0.31 [0.21, 0.41], <0.0001	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
EAP:n/N2 (%)	21/56 (37.5)	1/24 (4.2)	9/46 (19.6)	3/26 (11.5)	30/102 (29.4)	4/50 (8.0)
RR [95%-CI]; p-value	9.00 [1.28, 63.15], 0.0271		1.70 [0.50, 5.71], 0.3943		3.68 [1.37, 9.86], 0.0097	
OR [95%-CI]; p-value	13.80 [1.73, 109.79], 0.0022		1.86 [0.46, 7.61], 0.3800		4.79 [1.58, 14.49], 0.0029	
RD [95%-CI]; p-value	0.33 [0.18, 0.48], <0.0001		0.08 [-0.09, 0.25], 0.3490		0.21 [0.10, 0.33], 0.0003	
Vist 13/ET:n/N2 (%)	23/56 (41.1)	1/24 (4.2)	12/46 (26.1)	2/26 (7.7)	35/102 (34.3)	3/50 (6.0)
RR [95%-CI]; p-value	9.86 [1.41, 68.88], 0.0211		3.39 [0.82, 14.00], 0.0913		5.72 [1.85, 17.69], 0.0025	
OR [95%-CI]; p-value	16.03 [2.02, 127.25], 0.0010		4.24 [0.87, 20.68], 0.0582		8.18 [2.38, 28.19], 0.0002	
RD [95%-CI]; p-value	0.37 [0.22, 0.52], <0.0001		0.18 [0.02, 0.35], 0.0270		0.28 [0.17, 0.40], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_1_1_1_m_pth30pct_race.sas using SAS 9.4

Table 12.2.1.1.2.s4
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3403		0.0574		0.5560	
Vist 13/ET	0.9189		0.6621		0.8166	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
EAP:n/N1 (%)	52/85 (61.2)	13/48 (27.1)	70/98 (71.4)	10/46 (21.7)	122/183 (66.7)	23/94 (24.5)
RR [95%-CI]; p-value	2.26 [1.38, 3.70], 0.0012		3.29 [1.87, 5.77], <0.0001		2.72 [1.88, 3.94], <0.0001	
OR [95%-CI]; p-value	4.24 [1.96, 9.18], 0.0002		9.00 [3.94, 20.57], <0.0001		6.17 [3.52, 10.83], <0.0001	
RD [95%-CI]; p-value	0.34 [0.18, 0.50], <0.0001		0.50 [0.35, 0.65], <0.0001		0.42 [0.31, 0.53], <0.0001	
Vist 13/ET:n/N1 (%)	55/85 (64.7)	13/48 (27.1)	70/98 (71.4)	13/46 (28.3)	125/183 (68.3)	26/94 (27.7)
RR [95%-CI]; p-value	2.39 [1.46, 3.90], 0.0005		2.53 [1.57, 4.07], 0.0001		2.47 [1.76, 3.47], <0.0001	
OR [95%-CI]; p-value	4.94 [2.27, 10.73], <0.0001		6.35 [2.92, 13.80], <0.0001		5.64 [3.26, 9.76], <0.0001	
RD [95%-CI]; p-value	0.38 [0.21, 0.54], <0.0001		0.43 [0.27, 0.59], <0.0001		0.41 [0.29, 0.52], <0.0001	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
EAP:n/N2 (%)	35/56 (62.5)	4/24 (16.7)	20/46 (43.5)	8/26 (30.8)	55/102 (53.9)	12/50 (24.0)
RR [95%-CI]; p-value	3.75 [1.50, 9.38], 0.0047		1.41 [0.73, 2.75], 0.3075		2.25 [1.33, 3.80], 0.0025	
OR [95%-CI]; p-value	8.33 [2.50, 27.73], 0.0002		1.73 [0.63, 4.78], 0.2880		3.71 [1.74, 7.90], 0.0005	
RD [95%-CI]; p-value	0.46 [0.26, 0.65], <0.0001		0.13 [-0.10, 0.36], 0.2747		0.30 [0.15, 0.45], 0.0001	
Vist 13/ET:n/N2 (%)	35/56 (62.5)	6/24 (25.0)	26/46 (56.5)	7/26 (26.9)	61/102 (59.8)	13/50 (26.0)
RR [95%-CI]; p-value	2.50 [1.21, 5.15], 0.0129		2.10 [1.06, 4.15], 0.0331		2.30 [1.40, 3.77], 0.0009	
OR [95%-CI]; p-value	5.00 [1.71, 14.59], 0.0021		3.53 [1.24, 10.03], 0.0155		4.23 [2.01, 8.93], <0.0001	
RD [95%-CI]; p-value	0.38 [0.16, 0.59], 0.0006		0.30 [0.07, 0.52], 0.0092		0.34 [0.18, 0.49], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_1_1_2_m_pth10pct_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6507		0.6821		0.5744	
Comparison Baseline vs. EAP	0.0506		0.7088		0.0930	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	21.2 (4.66)	19.8 (5.42)	20.2 (5.32)	19.9 (5.51)	20.7 (5.03)	19.9 (5.43)
Visit 13/ET						
n/N1	78/85	45/48	91/98	40/46	169/183	85/94
Mean (SD)	65.1 (23.41)	17.8 (6.14)	68.0 (25.00)	20.6 (6.96)	66.6 (24.25)	19.1 (6.66)
EAP						
n/N1	67/85	42/48	87/98	39/46	154/183	81/94
Mean (SD)	68.2 (19.57)	17.9 (6.21)	68.8 (21.63)	20.5 (6.71)	68.5 (20.69)	19.2 (6.54)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.3 (2.15)	-2.5 (2.84)	47.8 (2.14)	0.4 (3.23)	45.9 (1.53)	-0.9 (2.15)
95% CI	[40.03, 48.56]	[-8.10, 3.15]	[43.53, 52.00]	[-5.98, 6.79]	[42.94, 48.95]	[-5.13, 3.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.77		47.36		46.84	
95% CI	[39.69, 53.85]		[39.69, 55.02]		[41.64, 52.03]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.40		2.31		2.37	
95% CI	[1.93, 2.87]		[1.85, 2.78]		[2.04, 2.70]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.6 (1.91)	-2.1 (2.41)	48.5 (1.87)	0.3 (2.79)	48.0 (1.35)	-0.8 (1.85)
95% CI	[43.80, 51.36]	[-6.89, 2.67]	[44.76, 52.16]	[-5.20, 5.85]	[45.31, 50.64]	[-4.47, 2.82]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.69		48.13		48.80	
95% CI	[43.58, 55.79]		[41.48, 54.78]		[44.29, 53.32]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.14		2.75		2.95	
95% CI	[2.57, 3.70]		[2.25, 3.26]		[2.57, 3.32]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	18.7 (5.35)	18.1 (5.41)	18.4 (5.91)	18.4 (5.49)	18.6 (5.58)	18.3 (5.40)
Visit 13/ET						
n/N2	53/56	23/24	41/46	22/26	94/102	45/50
Mean (SD)	65.2 (26.52)	17.0 (6.39)	60.7 (23.08)	18.5 (6.16)	63.2 (25.05)	17.8 (6.25)
EAP						
n/N2	51/56	22/24	37/46	22/26	88/102	44/50
Mean (SD)	65.5 (25.49)	17.1 (6.45)	62.0 (20.39)	17.6 (5.83)	64.0 (23.42)	17.4 (6.08)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.3 (2.90)	-0.9 (4.41)	42.0 (3.00)	-0.2 (4.09)	44.3 (2.14)	-0.9 (3.07)
95% CI	[40.55, 52.13]	[-9.68, 7.90]	[36.04, 48.03]	[-8.40, 7.98]	[40.11, 48.57]	[-6.92, 5.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.22		42.24		45.19	
95% CI	[36.69, 57.75]		[32.08, 52.40]		[37.79, 52.58]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.22		2.15		2.21	
95% CI	[1.62, 2.82]		[1.51, 2.78]		[1.77, 2.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.8 (2.90)	-1.0 (4.42)	44.0 (2.73)	-0.3 (3.54)	45.4 (2.06)	-0.7 (2.88)
95% CI	[41.01, 52.59]	[-9.78, 7.85]	[38.49, 49.42]	[-7.43, 6.74]	[41.32, 49.47]	[-6.41, 4.98]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.76		44.30		46.11	
95% CI	[37.22, 58.31]		[35.36, 53.24]		[39.10, 53.11]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.30		2.59		2.43	
95% CI	[1.68, 2.92]		[1.89, 3.29]		[1.97, 2.90]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.1.1.s4
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.6590		0.2814		0.2960	
Vist 13/ET	0.6557		0.3941		0.2391	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
EAP:n/N1 (%)	66/85 (77.6)	1/48 (2.1)	86/98 (87.8)	5/46 (10.9)	152/183 (83.1)	6/94 (6.4)
RR [95%-CI]; p-value	37.27 [5.34, 260.08], 0.0003		8.07 [3.52, 18.53], <0.0001		13.01 [5.98, 28.30], <0.0001	
OR [95%-CI]; p-value	163.26 [21.12, 1262.37], <0.0001		58.77 [19.41, 177.89], <0.0001		71.91 [28.87, 179.15], <0.0001	
RD [95%-CI]; p-value	0.76 [0.66, 0.85], <0.0001		0.77 [0.66, 0.88], <0.0001		0.77 [0.69, 0.84], <0.0001	
Vist 13/ET:n/N1 (%)	71/85 (83.5)	2/48 (4.2)	87/98 (88.8)	5/46 (10.9)	158/183 (86.3)	7/94 (7.4)
RR [95%-CI]; p-value	20.05 [5.15, 78.11], <0.0001		8.17 [3.56, 18.74], <0.0001		11.59 [5.67, 23.70], <0.0001	
OR [95%-CI]; p-value	116.64 [25.32, 537.24], <0.0001		64.85 [21.15, 198.86], <0.0001		78.55 [32.65, 189.00], <0.0001	
RD [95%-CI]; p-value	0.79 [0.70, 0.89], <0.0001		0.78 [0.67, 0.89], <0.0001		0.79 [0.72, 0.86], <0.0001	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
EAP:n/N2 (%)	47/56 (83.9)	1/24 (4.2)	34/46 (73.9)	0/26 (0.0)	81/102 (79.4)	1/50 (2.0)
RR [95%-CI]; p-value	20.14 [2.95, 137.68], 0.0022		39.17 [2.50, 613.33], 0.0090		39.71 [5.69, 277.07], 0.0002	
OR [95%-CI]; p-value	120.11 [14.34, 1006.01], <0.0001		147.33 [8.31, 2610.70], <0.0001		189.00 [24.64, 1449.47], <0.0001	
RD [95%-CI]; p-value	0.80 [0.67, 0.92], <0.0001		0.72 [0.58, 0.86], <0.0001		0.77 [0.69, 0.86], <0.0001	
Vist 13/ET:n/N2 (%)	46/56 (82.1)	0/24 (0.0)	36/46 (78.3)	1/26 (3.8)	82/102 (80.4)	1/50 (2.0)
RR [95%-CI]; p-value	40.25 [2.58, 627.16], 0.0084		20.35 [2.96, 139.90], 0.0022		40.20 [5.76, 280.45], 0.0002	
OR [95%-CI]; p-value	220.80 [12.36, 3944.49], <0.0001		90.00 [10.82, 748.31], <0.0001		200.90 [26.14, 1543.97], <0.0001	
RD [95%-CI]; p-value	0.80 [0.69, 0.92], <0.0001		0.74 [0.60, 0.88], <0.0001		0.78 [0.70, 0.87], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_1_1_m_25d30_race.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2904		0.8202		0.6735	
Comparison Baseline vs. EAP	0.1478		0.7728		0.5467	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	125.1 (38.50)	127.3 (33.29)	132.1 (38.72)	141.1 (55.98)	128.8 (38.65)	134.1 (46.09)
Visit 13/ET						
n/N1	62/71	35/36	72/80	29/35	134/151	64/71
Mean (SD)	100.3 (41.98)	136.9 (68.41)	98.8 (41.46)	139.1 (75.73)	99.5 (41.55)	137.9 (71.24)
EAP						
n/N1	58/71	33/36	69/80	30/35	127/151	63/71
Mean (SD)	95.8 (38.63)	133.4 (65.28)	98.3 (35.09)	138.6 (63.49)	97.2 (36.62)	135.9 (63.97)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-24.3 (6.02)	9.5 (8.02)	-30.4 (4.06)	-3.7 (6.43)	-27.5 (3.60)	3.2 (5.24)
95% CI	[-36.30, -12.38]	[-6.46, 25.40]	[-38.46, -22.34]	[-16.43, 9.09]	[-34.59, -20.38]	[-7.09, 13.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-33.81		-26.73		-30.72	
95% CI	[-53.74, -13.87]		[-41.89, -11.57]		[-43.29, -18.16]	
p-value	0.0011		0.0007		<0.0001	
Hedges' g	-0.65		-0.74		-0.70	
95% CI	[-1.08, -0.23]		[-1.18, -0.30]		[-1.01, -0.40]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.0 (5.57)	6.0 (7.38)	-30.0 (3.31)	-4.6 (5.06)	-29.6 (3.16)	0.9 (4.48)
95% CI	[-40.07, -17.94]	[-8.69, 20.65]	[-36.58, -23.42]	[-14.66, 5.43]	[-35.86, -23.40]	[-7.95, 9.74]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-34.98		-25.38		-30.52	
95% CI	[-53.37, -16.60]		[-37.48, -13.28]		[-41.38, -19.67]	
p-value	0.0003		<0.0001		<0.0001	
Hedges' g	-0.77		-0.80		-0.78	
95% CI	[-1.21, -0.33]		[-1.24, -0.36]		[-1.09, -0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	168.9 (62.30)	157.1 (52.45)	167.0 (82.39)	169.2 (67.06)	168.0 (72.32)	163.2 (60.19)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	127.1 (73.74)	161.2 (60.39)	137.1 (123.87)	196.2 (81.38)	131.8 (100.29)	178.9 (73.43)
EAP						
n/N2	59/70	31/36	55/64	31/37	114/134	62/73
Mean (SD)	123.1 (57.89)	159.7 (63.25)	131.7 (105.23)	174.9 (62.08)	127.2 (83.85)	167.3 (62.62)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-41.0 (6.32)	7.4 (9.04)	-26.4 (9.99)	25.2 (13.28)	-34.3 (5.84)	17.5 (8.03)
95% CI	[-53.58, -28.48]	[-10.52, 25.37]	[-46.23, -6.54]	[-1.13, 51.61]	[-45.81, -22.77]	[1.65, 33.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-48.45		-51.62		-51.78	
95% CI	[-70.45, -26.45]		[-84.64, -18.61]		[-71.38, -32.19]	
p-value	<0.0001		0.0025		<0.0001	
Hedges' g	-0.98		-0.67		-0.80	
95% CI	[-1.42, -0.55]		[-1.10, -0.24]		[-1.10, -0.49]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-40.3 (5.38)	9.6 (7.44)	-29.4 (8.28)	14.0 (11.03)	-35.0 (4.88)	12.2 (6.61)
95% CI	[-50.94, -29.57]	[-5.15, 24.43]	[-45.84, -12.91]	[-7.93, 35.94]	[-44.63, -25.39]	[-0.85, 25.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-49.89		-43.38		-47.21	
95% CI	[-68.23, -31.56]		[-70.81, -15.95]		[-63.44, -30.98]	
p-value	<0.0001		0.0023		<0.0001	
Hedges' g	-1.25		-0.70		-0.92	
95% CI	[-1.71, -0.78]		[-1.15, -0.25]		[-1.24, -0.60]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.1.1.1.s5
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4748		0.5992		0.3726	
Vist 13/ET	0.2266		0.2161		0.0867	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
EAP:n/N1 (%)	24/71 (33.8)	4/36 (11.1)	27/80 (33.8)	3/35 (8.6)	51/151 (33.8)	7/71 (9.9)
RR [95%-CI]; p-value	3.04 [1.14, 8.10], 0.0260		3.94 [1.28, 12.12], 0.0169		3.43 [1.64, 7.17], 0.0011	
OR [95%-CI]; p-value	4.09 [1.29, 12.90], 0.0116		5.43 [1.52, 19.37], 0.0047		4.66 [1.99, 10.91], 0.0002	
RD [95%-CI]; p-value	0.23 [0.08, 0.38], 0.0031		0.25 [0.11, 0.39], 0.0004		0.24 [0.14, 0.34], <0.0001	
Vist 13/ET:n/N1 (%)	26/71 (36.6)	5/36 (13.9)	29/80 (36.3)	5/35 (14.3)	55/151 (36.4)	10/71 (14.1)
RR [95%-CI]; p-value	2.64 [1.11, 6.29], 0.0288		2.54 [1.07, 6.01], 0.0342		2.59 [1.40, 4.77], 0.0023	
OR [95%-CI]; p-value	3.58 [1.24, 10.35], 0.0143		3.41 [1.19, 9.76], 0.0175		3.49 [1.66, 7.37], 0.0006	
RD [95%-CI]; p-value	0.23 [0.07, 0.39], 0.0051		0.22 [0.06, 0.38], 0.0060		0.22 [0.11, 0.33], <0.0001	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
EAP:n/N2 (%)	22/70 (31.4)	2/36 (5.6)	22/64 (34.4)	2/37 (5.4)	44/134 (32.8)	4/73 (5.5)
RR [95%-CI]; p-value	5.66 [1.41, 22.73], 0.0146		6.36 [1.58, 25.53], 0.0091		5.99 [2.24, 16.02], 0.0004	
OR [95%-CI]; p-value	7.79 [1.72, 35.37], 0.0026		9.17 [2.01, 41.72], 0.0010		8.43 [2.89, 24.60], <0.0001	
RD [95%-CI]; p-value	0.26 [0.13, 0.39], 0.0001		0.29 [0.15, 0.43], <0.0001		0.27 [0.18, 0.37], <0.0001	
Vist 13/ET:n/N2 (%)	28/70 (40.0)	2/36 (5.6)	32/64 (50.0)	3/37 (8.1)	60/134 (44.8)	5/73 (6.8)
RR [95%-CI]; p-value	7.20 [1.82, 28.54], 0.0050		6.17 [2.03, 18.75], 0.0013		6.54 [2.75, 15.55], <0.0001	
OR [95%-CI]; p-value	11.33 [2.52, 51.00], 0.0002		11.33 [3.16, 40.68], <0.0001		11.03 [4.18, 29.09], <0.0001	
RD [95%-CI]; p-value	0.34 [0.21, 0.48], <0.0001		0.42 [0.27, 0.57], <0.0001		0.38 [0.28, 0.48], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_1_1_1_m_pth30pct_ckd.sas using SAS 9.4

Table 12.2.1.1.2.s5
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3843		0.3457		0.1995	
Vist 13/ET	0.2673		0.7218		0.3047	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
EAP:n/N1 (%)	43/71 (60.6)	10/36 (27.8)	52/80 (65.0)	11/35 (31.4)	95/151 (62.9)	21/71 (29.6)
RR [95%-CI]; p-value	2.18 [1.25, 3.81], 0.0063		2.07 [1.24, 3.46], 0.0057		2.13 [1.46, 3.11], <0.0001	
OR [95%-CI]; p-value	3.99 [1.67, 9.54], 0.0014		4.05 [1.73, 9.47], 0.0009		4.04 [2.20, 7.41], <0.0001	
RD [95%-CI]; p-value	0.33 [0.14, 0.51], 0.0005		0.34 [0.15, 0.52], 0.0004		0.33 [0.20, 0.46], <0.0001	
Vist 13/ET:n/N1 (%)	42/71 (59.2)	11/36 (30.6)	56/80 (70.0)	11/35 (31.4)	98/151 (64.9)	22/71 (31.0)
RR [95%-CI]; p-value	1.94 [1.14, 3.29], 0.0144		2.23 [1.34, 3.71], 0.0021		2.09 [1.45, 3.02], <0.0001	
OR [95%-CI]; p-value	3.29 [1.40, 7.72], 0.0052		5.09 [2.16, 12.02], 0.0001		4.12 [2.25, 7.53], <0.0001	
RD [95%-CI]; p-value	0.29 [0.10, 0.47], 0.0030		0.39 [0.20, 0.57], <0.0001		0.34 [0.21, 0.47], <0.0001	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
EAP:n/N2 (%)	44/70 (62.9)	7/36 (19.4)	38/64 (59.4)	7/37 (18.9)	82/134 (61.2)	14/73 (19.2)
RR [95%-CI]; p-value	3.23 [1.62, 6.44], 0.0008		3.14 [1.56, 6.30], 0.0013		3.19 [1.96, 5.21], <0.0001	
OR [95%-CI]; p-value	7.01 [2.69, 18.26], <0.0001		6.26 [2.39, 16.39], <0.0001		6.65 [3.37, 13.10], <0.0001	
RD [95%-CI]; p-value	0.43 [0.26, 0.61], <0.0001		0.40 [0.23, 0.58], <0.0001		0.42 [0.30, 0.54], <0.0001	
Vist 13/ET:n/N2 (%)	48/70 (68.6)	8/36 (22.2)	40/64 (62.5)	9/37 (24.3)	88/134 (65.7)	17/73 (23.3)
RR [95%-CI]; p-value	3.09 [1.64, 5.80], 0.0005		2.57 [1.41, 4.68], 0.0020		2.82 [1.83, 4.35], <0.0001	
OR [95%-CI]; p-value	7.64 [3.00, 19.43], <0.0001		5.19 [2.10, 12.83], 0.0002		6.30 [3.29, 12.06], <0.0001	
RD [95%-CI]; p-value	0.46 [0.29, 0.64], <0.0001		0.38 [0.20, 0.56], <0.0001		0.42 [0.30, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_1_1_2_m_pth10pct_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7851		0.9940		0.8801	
Comparison Baseline vs. EAP	0.3711		0.4996		0.2700	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	20.8 (5.02)	19.5 (5.82)	19.9 (5.64)	18.8 (5.43)	20.3 (5.36)	19.2 (5.60)
Visit 13/ET						
n/N1	64/71	35/36	72/80	29/35	136/151	64/71
Mean (SD)	65.6 (25.91)	18.3 (6.59)	63.6 (22.57)	19.9 (6.44)	64.5 (24.13)	19.0 (6.52)
EAP						
n/N1	58/71	33/36	69/80	30/35	127/151	63/71
Mean (SD)	67.6 (23.96)	18.5 (6.73)	64.9 (21.10)	19.2 (6.04)	66.1 (22.40)	18.8 (6.37)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.8 (2.52)	-1.1 (3.42)	43.6 (2.24)	0.1 (3.53)	44.2 (1.68)	-0.6 (2.46)
95% CI	[39.77, 49.80]	[-7.85, 5.72]	[39.16, 48.06]	[-6.95, 7.08]	[40.92, 47.57]	[-5.44, 4.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.85		43.54		44.82	
95% CI	[37.40, 54.30]		[35.23, 51.85]		[38.93, 50.71]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.28		2.28		2.30	
95% CI	[1.76, 2.79]		[1.74, 2.81]		[1.92, 2.67]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (2.46)	-0.7 (3.27)	45.0 (2.09)	-0.1 (3.17)	46.0 (1.60)	-0.4 (2.27)
95% CI	[42.07, 51.86]	[-7.22, 5.78]	[40.87, 49.16]	[-6.35, 6.23]	[42.84, 49.17]	[-4.89, 4.07]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.69		45.07		46.42	
95% CI	[39.53, 55.85]		[37.53, 52.61]		[40.92, 51.91]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.55		2.59		2.59	
95% CI	[1.98, 3.11]		[2.03, 3.14]		[2.19, 2.98]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	19.7 (5.11)	18.9 (5.09)	19.4 (5.49)	19.9 (5.61)	19.5 (5.28)	19.4 (5.35)
Visit 13/ET						
n/N2	67/70	33/36	60/64	33/37	127/134	66/73
Mean (SD)	64.6 (23.50)	16.7 (5.69)	68.2 (26.75)	19.8 (7.05)	66.3 (25.05)	18.3 (6.56)
EAP						
n/N2	60/70	31/36	55/64	31/37	115/134	62/73
Mean (SD)	66.5 (20.66)	16.7 (5.67)	69.1 (21.77)	19.7 (7.02)	67.7 (21.14)	18.2 (6.50)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.2 (2.39)	-2.5 (3.41)	49.0 (2.77)	0.0 (3.74)	47.1 (1.82)	-1.1 (2.52)
95% CI	[40.50, 50.00]	[-9.24, 4.29]	[43.48, 54.48]	[-7.39, 7.45]	[43.47, 50.65]	[-6.09, 3.86]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.73		48.95		48.17	
95% CI	[39.45, 56.00]		[39.71, 58.20]		[42.03, 54.31]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.38		2.28		2.34	
95% CI	[1.85, 2.91]		[1.74, 2.81]		[1.96, 2.71]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.4 (2.18)	-2.5 (3.04)	49.8 (2.32)	0.2 (3.09)	48.6 (1.59)	-1.1 (2.16)
95% CI	[43.01, 51.69]	[-8.50, 3.57]	[45.15, 54.37]	[-5.93, 6.36]	[45.42, 51.69]	[-5.39, 3.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.81		49.55		49.67	
95% CI	[42.39, 57.24]		[41.86, 57.23]		[44.38, 54.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.92		2.87		2.92	
95% CI	[2.32, 3.53]		[2.26, 3.48]		[2.48, 3.35]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.1.1.s5
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3487		0.2206		0.7533	
Vist 13/ET	0.9431		0.4776		0.5618	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
EAP:n/N1 (%)	55/71 (77.5)	2/36 (5.6)	67/80 (83.8)	1/35 (2.9)	122/151 (80.8)	3/71 (4.2)
RR [95%-CI]; p-value	13.94 [3.61, 53.93], 0.0001		29.31 [4.24, 202.79], 0.0006		19.12 [6.30, 58.03], <0.0001	
OR [95%-CI]; p-value	58.44 [12.64, 270.12], <0.0001		175.23 [21.99, 1396.19], <0.0001		95.36 [28.01, 324.65], <0.0001	
RD [95%-CI]; p-value	0.72 [0.60, 0.84], <0.0001		0.81 [0.71, 0.91], <0.0001		0.77 [0.69, 0.84], <0.0001	
Vist 13/ET:n/N1 (%)	56/71 (78.9)	1/36 (2.8)	67/80 (83.8)	2/35 (5.7)	123/151 (81.5)	3/71 (4.2)
RR [95%-CI]; p-value	28.39 [4.10, 196.86], 0.0007		14.66 [3.80, 56.49], <0.0001		19.28 [6.35, 58.50], <0.0001	
OR [95%-CI]; p-value	130.67 [16.52, 1033.26], <0.0001		85.04 [18.12, 399.04], <0.0001		99.57 [29.19, 339.62], <0.0001	
RD [95%-CI]; p-value	0.76 [0.65, 0.87], <0.0001		0.78 [0.67, 0.89], <0.0001		0.77 [0.69, 0.85], <0.0001	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
EAP:n/N2 (%)	58/70 (82.9)	0/36 (0.0)	53/64 (82.8)	4/37 (10.8)	111/134 (82.8)	4/73 (5.5)
RR [95%-CI]; p-value	60.49 [3.85, 950.73], 0.0035		7.66 [3.02, 19.46], <0.0001		15.12 [5.81, 39.32], <0.0001	
OR [95%-CI]; p-value	348.00 [19.94, 6072.76], <0.0001		39.75 [11.69, 135.20], <0.0001		83.25 [27.62, 250.97], <0.0001	
RD [95%-CI]; p-value	0.81 [0.72, 0.91], <0.0001		0.72 [0.58, 0.86], <0.0001		0.77 [0.69, 0.86], <0.0001	
Vist 13/ET:n/N2 (%)	61/70 (87.1)	1/36 (2.8)	56/64 (87.5)	4/37 (10.8)	117/134 (87.3)	5/73 (6.8)
RR [95%-CI]; p-value	31.37 [4.53, 217.14], 0.0005		8.09 [3.19, 20.52], <0.0001		12.75 [5.46, 29.78], <0.0001	
OR [95%-CI]; p-value	237.22 [28.84, 1951.53], <0.0001		57.75 [16.14, 206.66], <0.0001		93.60 [33.05, 265.07], <0.0001	
RD [95%-CI]; p-value	0.84 [0.75, 0.94], <0.0001		0.77 [0.64, 0.90], <0.0001		0.80 [0.72, 0.89], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_1_1_m_25d30_ckd.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4445		0.7408		0.9618	
Comparison Baseline vs. EAP	0.0520		0.7196		0.3442	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	97.9 (9.56)	100.3 (9.79)	99.6 (9.03)	102.7 (7.22)	98.9 (9.26)	101.3 (8.76)
Visit 13/ET						
n/N1	39/43	25/26	50/53	18/20	89/96	43/46
Mean (SD)	84.6 (40.23)	111.0 (41.97)	77.4 (29.69)	111.3 (41.71)	80.6 (34.68)	111.1 (41.36)
EAP						
n/N1	36/43	24/26	49/53	17/20	85/96	41/46
Mean (SD)	84.4 (35.82)	103.4 (34.83)	79.7 (29.73)	108.7 (25.78)	81.7 (32.33)	105.6 (31.15)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-13.1 (6.48)	10.4 (8.12)	-22.2 (4.59)	8.6 (7.69)	-17.6 (3.89)	9.5 (5.65)
95% CI	[-26.08, -0.15]	[-5.81, 26.66]	[-31.32, -13.01]	[-6.78, 23.94]	[-25.33, -9.94]	[-1.67, 20.69]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-23.54		-30.74		-27.15	
95% CI	[-44.44, -2.64]		[-48.72, -12.77]		[-40.80, -13.50]	
p-value	0.0279		0.0011		0.0001	
Hedges' g	-0.58		-0.95		-0.76	
95% CI	[-1.08, -0.07]		[-1.50, -0.39]		[-1.14, -0.39]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-13.2 (5.59)	2.7 (6.86)	-19.8 (3.80)	4.9 (6.49)	-16.5 (3.29)	3.8 (4.77)
95% CI	[-24.43, -2.04]	[-11.01, 16.45]	[-27.43, -12.24]	[-8.10, 17.85]	[-23.03, -10.00]	[-5.62, 13.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-15.96		-24.71		-20.34	
95% CI	[-33.74, 1.82]		[-39.81, -9.60]		[-31.86, -8.82]	
p-value	0.0776		0.0018		0.0007	
Hedges' g	-0.49		-0.96		-0.72	
95% CI	[-1.01, 0.02]		[-1.53, -0.39]		[-1.10, -0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	133.1 (10.45)	133.1 (12.01)	132.5 (12.32)	135.0 (11.41)	132.8 (11.31)	134.2 (11.59)
Visit 13/ET						
n/N2	46/50	22/22	42/44	23/28	88/94	45/50
Mean (SD)	102.6 (32.28)	133.5 (39.56)	111.7 (39.57)	146.2 (57.90)	107.0 (36.03)	140.0 (49.64)
EAP						
n/N2	43/50	22/22	40/44	23/28	83/94	45/50
Mean (SD)	97.8 (27.58)	137.1 (33.13)	110.5 (34.02)	142.5 (39.65)	103.9 (31.32)	139.9 (36.29)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.6 (5.12)	0.3 (7.41)	-20.5 (6.86)	11.3 (9.28)	-25.8 (4.36)	6.4 (6.09)
95% CI	[-40.78, -20.32]	[-14.49, 15.11]	[-34.22, -6.78]	[-7.23, 29.88]	[-34.44, -17.21]	[-5.68, 18.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-30.86		-31.83		-32.19	
95% CI	[-48.85, -12.87]		[-54.94, -8.72]		[-47.01, -17.38]	
p-value	0.0011		0.0077		<0.0001	
Hedges' g	-0.81		-0.72		-0.78	
95% CI	[-1.34, -0.29]		[-1.24, -0.21]		[-1.15, -0.41]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-35.9 (4.47)	3.8 (6.25)	-22.2 (5.33)	9.0 (7.03)	-29.1 (3.48)	6.5 (4.72)
95% CI	[-44.86, -26.98]	[-8.74, 16.26]	[-32.83, -11.51]	[-5.10, 23.02]	[-36.02, -22.25]	[-2.82, 15.87]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-39.68		-31.13		-35.66	
95% CI	[-55.05, -24.31]		[-48.78, -13.49]		[-47.26, -24.05]	
p-value	<0.0001		0.0008		<0.0001	
Hedges' g	-1.33		-0.92		-1.12	
95% CI	[-1.89, -0.78]		[-1.45, -0.39]		[-1.51, -0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	205.0 (57.47)	195.9 (35.37)	215.8 (70.38)	223.6 (65.71)	210.4 (64.07)	209.8 (54.04)
Visit 13/ET						
n/N3	44/48	21/24	40/47	22/24	84/95	43/48
Mean (SD)	152.5 (80.19)	209.4 (68.08)	169.3 (141.35)	242.6 (80.42)	160.5 (113.10)	226.4 (75.65)
EAP						
n/N3	38/48	18/24	35/47	21/24	73/95	39/48
Mean (SD)	146.7 (62.24)	214.0 (72.02)	162.8 (119.69)	212.1 (70.37)	154.4 (93.92)	213.0 (70.20)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-53.2 (9.94)	14.6 (14.43)	-43.0 (13.80)	11.5 (18.64)	-49.4 (8.55)	15.6 (11.94)
95% CI	[-73.03, -33.27]		[-70.60, -15.38]		[-66.30, -32.46]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-67.75		-54.52		-65.01	
95% CI	[-102.92, -32.59]		[-101.04, -8.01]		[-94.07, -35.94]	
p-value	0.0003		0.0224		<0.0001	
Hedges' g	-1.06		-0.65		-0.84	
95% CI	[-1.60, -0.51]		[-1.18, -0.13]		[-1.22, -0.46]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-53.4 (9.12)	19.0 (13.27)	-50.0 (11.76)	-3.4 (15.19)	-52.0 (7.47)	8.5 (10.25)
95% CI	[-71.74, -35.14]		[-73.56, -26.37]		[-66.86, -37.23]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-72.46		-46.57		-60.57	
95% CI	[-104.79, -40.13]		[-85.11, -8.04]		[-85.71, -35.42]	
p-value	<0.0001		0.0188		<0.0001	
Hedges' g	-1.29		-0.66		-0.94	
95% CI	[-1.89, -0.69]		[-1.21, -0.12]		[-1.34, -0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.1.1.1.s6
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.5024		0.8412		0.8755	
Vist 13/ET	0.4599		0.6414		0.3316	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
EAP:n/N1 (%)	11/43 (25.6)	3/26 (11.5)	19/53 (35.8)	1/20 (5.0)	30/96 (31.3)	4/46 (8.7)
RR [95%-CI]; p-value	2.22 [0.68, 7.22], 0.1861		7.17 [1.03, 50.09], 0.0470		3.59 [1.35, 9.60], 0.0107	
OR [95%-CI]; p-value	2.64 [0.66, 10.52], 0.1598		10.62 [1.32, 85.65], 0.0084		4.77 [1.57, 14.52], 0.0032	
RD [95%-CI]; p-value	0.14 [-0.04, 0.32], 0.1244		0.31 [0.15, 0.47], 0.0002		0.23 [0.10, 0.35], 0.0003	
Vist 13/ET:n/N1 (%)	13/43 (30.2)	3/26 (11.5)	24/53 (45.3)	3/20 (15.0)	37/96 (38.5)	6/46 (13.0)
RR [95%-CI]; p-value	2.62 [0.82, 8.33], 0.1028		3.02 [1.02, 8.93], 0.0458		2.95 [1.34, 6.50], 0.0070	
OR [95%-CI]; p-value	3.32 [0.85, 13.05], 0.0746		4.69 [1.23, 17.93], 0.0168		4.18 [1.61, 10.83], 0.0020	
RD [95%-CI]; p-value	0.19 [0.00, 0.37], 0.0467		0.30 [0.10, 0.51], 0.0040		0.25 [0.12, 0.39], 0.0003	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
EAP:n/N2 (%)	19/50 (38.0)	1/22 (4.5)	11/44 (25.0)	2/28 (7.1)	30/94 (31.9)	3/50 (6.0)
RR [95%-CI]; p-value	8.36 [1.19, 58.60], 0.0326		3.50 [0.84, 14.63], 0.0860		5.32 [1.71, 16.57], 0.0039	
OR [95%-CI]; p-value	12.87 [1.60, 103.62], 0.0035		4.33 [0.88, 21.29], 0.0548		7.34 [2.11, 25.51], 0.0004	
RD [95%-CI]; p-value	0.33 [0.17, 0.49], <0.0001		0.18 [0.02, 0.34], 0.0283		0.26 [0.14, 0.37], <0.0001	
Vist 13/ET:n/N2 (%)	20/50 (40.0)	3/22 (13.6)	13/44 (29.5)	3/28 (10.7)	33/94 (35.1)	6/50 (12.0)
RR [95%-CI]; p-value	2.93 [0.97, 8.86], 0.0563		2.76 [0.86, 8.82], 0.0872		2.93 [1.32, 6.51], 0.0085	
OR [95%-CI]; p-value	4.22 [1.10, 16.17], 0.0271		3.49 [0.90, 13.64], 0.0610		3.97 [1.53, 10.28], 0.0030	
RD [95%-CI]; p-value	0.26 [0.07, 0.46], 0.0089		0.19 [0.01, 0.37], 0.0370		0.23 [0.10, 0.36], 0.0006	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_1_m_pth30pct_ttlpth.sas using SAS 9.4

Table 12.2.1.1.1.s6
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
EAP:n/N3 (%)	16/48 (33.3)	2/24 (8.3)	19/47 (40.4)	2/24 (8.3)	35/95 (36.8)	4/48 (8.3)
RR [95%-CI]; p-value	4.00 [1.00, 15.99], 0.0499		4.85 [1.23, 19.12], 0.0240		4.42 [1.67, 11.72], 0.0028	
OR [95%-CI]; p-value	5.50 [1.15, 26.36], 0.0209		7.46 [1.57, 35.53], 0.0051		6.42 [2.12, 19.38], 0.0003	
RD [95%-CI]; p-value	0.25 [0.08, 0.42], 0.0047		0.32 [0.14, 0.50], 0.0004		0.29 [0.16, 0.41], <0.0001	
Vist 13/ET:n/N3 (%)	21/48 (43.8)	1/24 (4.2)	24/47 (51.1)	2/24 (8.3)	45/95 (47.4)	3/48 (6.3)
RR [95%-CI]; p-value	10.50 [1.50, 73.46], 0.0178		6.13 [1.58, 23.78], 0.0088		7.58 [2.48, 23.13], 0.0004	
OR [95%-CI]; p-value	17.89 [2.23, 143.44], 0.0006		11.48 [2.42, 54.43], 0.0004		13.50 [3.92, 46.47], <0.0001	
RD [95%-CI]; p-value	0.40 [0.23, 0.56], <0.0001		0.43 [0.25, 0.61], <0.0001		0.41 [0.29, 0.53], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_1_m_pth30pct_ttlpth.sas using SAS 9.4

Table 12.2.1.1.2.s6
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4174		0.7153		0.6286	
Vist 13/ET	0.4930		0.6427		0.4158	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
EAP:n/N1 (%)	25/43 (58.1)	8/26 (30.8)	37/53 (69.8)	6/20 (30.0)	62/96 (64.6)	14/46 (30.4)
RR [95%-CI]; p-value	1.89 [1.01, 3.55], 0.0477		2.33 [1.16, 4.65], 0.0168		2.12 [1.34, 3.37], 0.0014	
OR [95%-CI]; p-value	3.13 [1.12, 8.75], 0.0274		5.40 [1.76, 16.57], 0.0020		4.17 [1.96, 8.86], 0.0001	
RD [95%-CI]; p-value	0.27 [0.04, 0.50], 0.0200		0.40 [0.16, 0.63], 0.0009		0.34 [0.18, 0.51], <0.0001	
Vist 13/ET:n/N1 (%)	27/43 (62.8)	7/26 (26.9)	36/53 (67.9)	7/20 (35.0)	63/96 (65.6)	14/46 (30.4)
RR [95%-CI]; p-value	2.33 [1.19, 4.57], 0.0138		1.94 [1.04, 3.63], 0.0377		2.16 [1.36, 3.42], 0.0011	
OR [95%-CI]; p-value	4.58 [1.58, 13.28], 0.0039		3.93 [1.33, 11.64], 0.0108		4.36 [2.05, 9.30], <0.0001	
RD [95%-CI]; p-value	0.36 [0.14, 0.58], 0.0017		0.33 [0.09, 0.57], 0.0082		0.35 [0.19, 0.52], <0.0001	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
EAP:n/N2 (%)	36/50 (72.0)	6/22 (27.3)	25/44 (56.8)	5/28 (17.9)	61/94 (64.9)	11/50 (22.0)
RR [95%-CI]; p-value	2.64 [1.31, 5.34], 0.0069		3.18 [1.38, 7.33], 0.0066		2.95 [1.71, 5.08], <0.0001	
OR [95%-CI]; p-value	6.86 [2.23, 21.08], 0.0004		6.05 [1.94, 18.86], 0.0011		6.55 [2.97, 14.47], <0.0001	
RD [95%-CI]; p-value	0.45 [0.22, 0.67], <0.0001		0.39 [0.19, 0.59], 0.0002		0.43 [0.28, 0.58], <0.0001	
Vist 13/ET:n/N2 (%)	34/50 (68.0)	8/22 (36.4)	29/44 (65.9)	8/28 (28.6)	63/94 (67.0)	16/50 (32.0)
RR [95%-CI]; p-value	1.87 [1.04, 3.36], 0.0358		2.31 [1.24, 4.30], 0.0085		2.09 [1.36, 3.21], 0.0007	
OR [95%-CI]; p-value	3.72 [1.30, 10.65], 0.0121		4.83 [1.73, 13.54], 0.0020		4.32 [2.07, 8.99], <0.0001	
RD [95%-CI]; p-value	0.32 [0.08, 0.56], 0.0095		0.37 [0.16, 0.59], 0.0008		0.35 [0.19, 0.51], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_2_m_pth10pct_ttlpth.sas using SAS 9.4

Table 12.2.1.1.2.s6
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
EAP:n/N3 (%)	26/48 (54.2)	3/24 (12.5)	28/47 (59.6)	7/24 (29.2)	54/95 (56.8)	10/48 (20.8)
RR [95%-CI]; p-value	4.33 [1.46, 12.89], 0.0084		2.04 [1.05, 3.98], 0.0357		2.73 [1.53, 4.87], 0.0007	
OR [95%-CI]; p-value	8.27 [2.17, 31.48], 0.0007		3.58 [1.25, 10.28], 0.0153		5.00 [2.23, 11.21], <0.0001	
RD [95%-CI]; p-value	0.42 [0.22, 0.61], <0.0001		0.30 [0.07, 0.53], 0.0095		0.36 [0.21, 0.51], <0.0001	
Vist 13/ET:n/N3 (%)	29/48 (60.4)	4/24 (16.7)	31/47 (66.0)	5/24 (20.8)	60/95 (63.2)	9/48 (18.8)
RR [95%-CI]; p-value	3.63 [1.44, 9.13], 0.0063		3.17 [1.41, 7.09], 0.0051		3.37 [1.83, 6.19], <0.0001	
OR [95%-CI]; p-value	7.63 [2.25, 25.84], 0.0004		7.36 [2.32, 23.37], 0.0003		7.43 [3.22, 17.14], <0.0001	
RD [95%-CI]; p-value	0.44 [0.23, 0.64], <0.0001		0.45 [0.24, 0.66], <0.0001		0.44 [0.30, 0.59], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_2_m_pth10pct_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4366		0.6279		0.2655	
Comparison Baseline vs. EAP	0.9219		0.9898		0.9316	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	20.8 (5.29)	20.8 (5.88)	20.6 (5.26)	21.2 (5.13)	20.6 (5.25)	21.0 (5.51)
Visit 13/ET						
n/N1	40/43	25/26	50/53	18/20	90/96	43/46
Mean (SD)	67.1 (26.33)	18.1 (6.80)	69.1 (22.52)	20.4 (5.37)	68.2 (24.16)	19.1 (6.28)
EAP						
n/N1	36/43	24/26	49/53	17/20	85/96	41/46
Mean (SD)	66.7 (23.64)	18.3 (6.61)	69.8 (20.67)	20.8 (6.31)	68.5 (21.89)	19.3 (6.52)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.6 (3.21)	-2.9 (4.06)	48.1 (2.78)	-0.9 (4.63)	47.3 (2.12)	-2.0 (3.09)
95% CI	[40.13, 52.97]	[-11.00, 5.24]	[42.56, 53.65]	[-10.20, 8.32]	[43.15, 51.54]	[-8.11, 4.12]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.43		49.05		49.34	
95% CI	[39.08, 59.78]		[38.25, 59.85]		[41.92, 56.76]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.42		2.49		2.50	
95% CI	[1.77, 3.07]		[1.81, 3.16]		[2.03, 2.97]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.4 (3.01)	-2.5 (3.68)	49.2 (2.54)	-0.8 (4.33)	47.8 (1.96)	-1.7 (2.83)
95% CI	[40.41, 52.46]	[-9.87, 4.89]	[44.09, 54.26]	[-9.41, 7.88]	[43.93, 51.69]	[-7.26, 3.95]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.92		49.94		49.46	
95% CI	[39.40, 58.45]		[39.89, 59.98]		[42.64, 56.29]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.70		2.80		2.80	
95% CI	[2.00, 3.40]		[2.08, 3.53]		[2.30, 3.31]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	19.8 (4.45)	17.7 (5.49)	20.5 (5.85)	19.1 (5.31)	20.2 (5.14)	18.5 (5.38)
Visit 13/ET						
n/N2	47/50	22/22	42/44	23/28	89/94	45/50
Mean (SD)	66.8 (21.74)	16.2 (5.76)	60.2 (19.67)	20.5 (6.81)	63.7 (20.94)	18.4 (6.61)
EAP						
n/N2	44/50	22/22	40/44	23/28	84/94	45/50
Mean (SD)	69.0 (20.79)	16.6 (6.28)	60.2 (18.55)	19.4 (5.77)	64.8 (20.13)	18.1 (6.12)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	47.5 (2.71)	-2.6 (3.99)	40.1 (2.51)	0.6 (3.39)	43.8 (1.85)	-0.9 (2.60)
95% CI	[42.10, 52.91]	[-10.59, 5.34]	[35.08, 45.10]	[-6.13, 7.42]	[40.10, 47.41]	[-6.02, 4.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.13		39.45		44.63	
95% CI	[40.41, 59.85]		[31.02, 47.87]		[38.30, 50.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.56		2.37		2.47	
95% CI	[1.90, 3.22]		[1.72, 3.02]		[2.01, 2.93]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	49.8 (2.66)	-2.1 (3.79)	40.1 (2.30)	0.1 (3.03)	44.9 (1.77)	-0.8 (2.42)
95% CI	[44.46, 55.08]	[-9.64, 5.49]	[35.53, 44.71]	[-5.94, 6.19]	[41.37, 48.37]	[-5.59, 3.99]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.84		39.99		45.67	
95% CI	[42.52, 61.17]		[32.38, 47.61]		[39.71, 51.63]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.79		2.74		2.72	
95% CI	[2.10, 3.49]		[2.04, 3.43]		[2.23, 3.21]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	20.1 (5.55)	19.0 (4.56)	17.8 (5.26)	18.1 (5.86)	19.0 (5.50)	18.6 (5.21)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	61.5 (26.02)	18.1 (5.91)	67.2 (30.58)	18.7 (7.75)	64.2 (28.26)	18.4 (6.81)
EAP						
n/N3	38/48	18/24	35/47	21/24	73/95	39/48
Mean (SD)	65.1 (22.95)	18.0 (5.92)	70.0 (24.22)	18.4 (7.48)	67.4 (23.53)	18.2 (6.72)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	41.6 (3.19)	-0.7 (4.62)	49.9 (3.73)	-0.0 (5.15)	45.6 (2.44)	-0.1 (3.44)
95% CI	[35.18, 47.92]		[42.42, 57.34]		[40.80, 50.45]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.23		49.91		45.77	
95% CI	[30.99, 53.47]		[37.17, 62.66]		[37.42, 54.12]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.00		2.05		2.02	
95% CI	[1.38, 2.61]		[1.41, 2.69]		[1.58, 2.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	45.5 (2.90)	-1.1 (4.21)	52.1 (3.13)	0.9 (4.04)	48.8 (2.12)	-0.1 (2.91)
95% CI	[39.69, 51.31]		[45.86, 58.42]		[44.61, 53.03]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.62		51.26		48.94	
95% CI	[36.36, 56.88]		[41.01, 61.52]		[41.80, 56.08]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.58		2.74		2.67	
95% CI	[1.85, 3.32]		[2.01, 3.48]		[2.15, 3.19]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.1.1.s6
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.9306		0.3432		0.4963	
Vist 13/ET	0.8627		0.4837		0.3812	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
EAP:n/N1 (%)	35/43 (81.4)	1/26 (3.8)	49/53 (92.5)	2/20 (10.0)	84/96 (87.5)	3/46 (6.5)
RR [95%-CI]; p-value	21.16 [3.08, 145.39], 0.0019		9.25 [2.48, 34.51], 0.0009		13.42 [4.48, 40.17], <0.0001	
OR [95%-CI]; p-value	109.38 [12.85, 930.81], <0.0001		110.25 [18.57, 654.59], <0.0001		100.33 [26.87, 374.63], <0.0001	
RD [95%-CI]; p-value	0.78 [0.64, 0.91], <0.0001		0.82 [0.68, 0.97], <0.0001		0.81 [0.71, 0.91], <0.0001	
Vist 13/ET:n/N1 (%)	36/43 (83.7)	0/26 (0.0)	49/53 (92.5)	1/20 (5.0)	85/96 (88.5)	1/46 (2.2)
RR [95%-CI]; p-value	44.37 [2.84, 693.19], 0.0068		18.49 [2.73, 125.10], 0.0028		40.73 [5.85, 283.39], 0.0002	
OR [95%-CI]; p-value	267.43 [14.52, 4924.38], <0.0001		232.75 [24.42, 2218.05], <0.0001		347.73 [43.50, 2779.92], <0.0001	
RD [95%-CI]; p-value	0.82 [0.70, 0.94], <0.0001		0.87 [0.76, 0.99], <0.0001		0.86 [0.79, 0.94], <0.0001	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
EAP:n/N2 (%)	43/50 (86.0)	1/22 (4.5)	38/44 (86.4)	0/28 (0.0)	81/94 (86.2)	1/50 (2.0)
RR [95%-CI]; p-value	18.92 [2.78, 128.82], 0.0027		49.23 [3.15, 769.96], 0.0055		43.09 [6.18, 300.41], 0.0001	
OR [95%-CI]; p-value	129.00 [14.89, 1117.77], <0.0001		354.67 [19.01, 6615.52], <0.0001		305.31 [38.73, 2406.60], <0.0001	
RD [95%-CI]; p-value	0.81 [0.68, 0.94], <0.0001		0.85 [0.73, 0.96], <0.0001		0.84 [0.76, 0.92], <0.0001	
Vist 13/ET:n/N2 (%)	43/50 (86.0)	1/22 (4.5)	40/44 (90.9)	2/28 (7.1)	83/94 (88.3)	3/50 (6.0)
RR [95%-CI]; p-value	18.92 [2.78, 128.82], 0.0027		12.73 [3.34, 48.55], 0.0002		14.72 [4.90, 44.19], <0.0001	
OR [95%-CI]; p-value	129.00 [14.89, 1117.77], <0.0001		130.00 [22.19, 761.48], <0.0001		118.21 [31.40, 445.09], <0.0001	
RD [95%-CI]; p-value	0.81 [0.68, 0.94], <0.0001		0.84 [0.71, 0.97], <0.0001		0.82 [0.73, 0.92], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_1_1_m_25d30_ttlpth.sas using SAS 9.4

Table 12.3.1.1.s6
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
EAP:n/N3 (%)	35/48 (72.9)	0/24 (0.0)	33/47 (70.2)	3/24 (12.5)	68/95 (71.6)	3/48 (6.3)
RR [95%-CI]; p-value	35.73 [2.29, 558.22], 0.0108		5.62 [1.92, 16.45], 0.0016		11.45 [3.80, 34.51], <0.0001	
OR [95%-CI]; p-value	129.23 [7.31, 2283.75], <0.0001		16.50 [4.23, 64.40], <0.0001		37.78 [10.81, 131.97], <0.0001	
RD [95%-CI]; p-value	0.71 [0.57, 0.85], <0.0001		0.58 [0.39, 0.76], <0.0001		0.65 [0.54, 0.77], <0.0001	
Vist 13/ET:n/N3 (%)	38/48 (79.2)	1/24 (4.2)	34/47 (72.3)	3/24 (12.5)	72/95 (75.8)	4/48 (8.3)
RR [95%-CI]; p-value	19.00 [2.77, 130.14], 0.0027		5.79 [1.98, 16.93], 0.0013		9.09 [3.53, 23.40], <0.0001	
OR [95%-CI]; p-value	87.40 [10.49, 728.02], <0.0001		18.31 [4.66, 71.92], <0.0001		34.43 [11.17, 106.18], <0.0001	
RD [95%-CI]; p-value	0.75 [0.61, 0.89], <0.0001		0.60 [0.41, 0.78], <0.0001		0.67 [0.56, 0.79], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_1_1_m_25d30_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4687		0.7147		0.8175	
Comparison Baseline vs. EAP	0.2586		0.3813		0.2129	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	142.4 (71.43)	99.7 (11.50)	122.2 (55.07)	116.4 (30.00)	129.4 (61.52)	108.1 (23.15)
Visit 13/ET						
n/N1	17/18	5/5	30/32	4/5	47/50	9/10
Mean (SD)	120.9 (74.37)	106.4 (45.36)	86.9 (38.25)	105.8 (35.28)	99.2 (55.85)	106.1 (38.67)
EAP						
n/N1	14/18	5/5	30/32	4/5	44/50	9/10
Mean (SD)	128.1 (65.16)	96.5 (41.58)	89.3 (38.10)	104.9 (20.58)	101.6 (50.96)	100.2 (32.30)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-20.9 (14.46)	-7.4 (27.36)	-26.9 (6.06)	1.0 (16.74)	-23.1 (6.85)	-2.6 (15.18)
95% CI	[-51.13, 9.42]	[-64.66, 49.88]	[-39.30, -14.59]	[-33.16, 35.12]	[-36.88, -9.38]	[-33.05, 27.92]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-13.46		-27.93		-20.57	
95% CI	[-79.29, 52.36]		[-64.32, 8.46]		[-54.41, 13.27]	
p-value	0.6734		0.1277		0.2279	
Hedges' g	-0.48		-0.88		-0.67	
95% CI	[-1.45, 0.49]		[-1.92, 0.16]		[-1.38, 0.04]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-21.9 (12.09)	-18.1 (20.92)	-25.0 (6.13)	-13.9 (16.83)	-22.2 (6.15)	-14.6 (12.58)
95% CI	[-47.58, 3.68]	[-62.44, 26.24]	[-37.53, -12.55]	[-48.19, 20.46]	[-34.56, -9.83]	[-39.89, 10.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-3.84		-11.17		-7.60	
95% CI	[-56.42, 48.73]		[-47.73, 25.38]		[-36.06, 20.86]	
p-value	0.8787		0.5376		0.5938	
Hedges' g	-0.47		-0.25		-0.42	
95% CI	[-1.45, 0.52]		[-1.27, 0.77]		[-1.13, 0.29]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	143.6 (47.03)	144.7 (45.21)	152.4 (66.36)	155.1 (57.67)	147.8 (57.08)	149.8 (51.76)
Visit 13/ET						
n/N2	105/108	62/63	94/98	57/61	199/206	119/124
Mean (SD)	111.0 (58.03)	153.2 (65.59)	120.3 (98.75)	167.4 (76.02)	115.4 (79.82)	160.0 (70.83)
EAP						
n/N2	103/108	59/63	94/98	57/61	197/206	116/124
Mean (SD)	107.0 (48.56)	150.3 (65.28)	120.7 (83.69)	160.7 (65.43)	113.6 (67.80)	155.4 (65.28)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.7 (4.65)	10.1 (6.05)	-32.1 (6.63)	11.5 (8.51)	-31.9 (3.99)	10.9 (5.16)
95% CI	[-40.91, -22.54]	[-1.85, 22.05]	[-45.21, -19.02]	[-5.29, 28.35]	[-39.79, -24.08]	[0.72, 21.03]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-41.83		-43.64		-42.81	
95% CI	[-56.90, -26.75]		[-64.97, -22.32]		[-55.66, -29.97]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.86		-0.68		-0.76	
95% CI	[-1.19, -0.54]		[-1.01, -0.34]		[-0.99, -0.52]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-35.9 (4.08)	9.0 (5.38)	-30.8 (5.05)	5.4 (6.49)	-33.4 (3.23)	7.3 (4.20)
95% CI	[-43.90, -27.81]	[-1.66, 19.61]	[-40.76, -20.79]	[-7.39, 18.26]	[-39.71, -27.01]	[-0.93, 15.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.83		-36.21		-40.70	
95% CI	[-58.17, -31.49]		[-52.46, -19.96]		[-51.12, -30.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.07		-0.73		-0.89	
95% CI	[-1.41, -0.73]		[-1.07, -0.39]		[-1.13, -0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.1.1.1.s7

Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH

ITT Population

Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0641		0.2408		0.0560	
Vist 13/ET	0.4420		0.5878		0.3751	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
EAP:n/N1 (%)	2/18 (11.1)	1/5 (20.0)	11/32 (34.4)	1/5 (20.0)	13/50 (26.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		1.72 [0.28, 10.58], 0.5591		1.30 [0.35, 4.89], 0.6979	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		2.10 [0.21, 21.10], 0.5231		1.41 [0.26, 7.49], 0.6892	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		0.14 [-0.24, 0.53], 0.4670		0.06 [-0.22, 0.34], 0.6702	
Vist 13/ET:n/N1 (%)	7/18 (38.9)	1/5 (20.0)	15/32 (46.9)	1/5 (20.0)	22/50 (44.0)	2/10 (20.0)
RR [95%-CI]; p-value	1.94 [0.31, 12.32], 0.4802		2.34 [0.39, 14.06], 0.3514		2.20 [0.61, 7.90], 0.2267	
OR [95%-CI]; p-value	2.55 [0.23, 27.71], 0.4327		3.53 [0.35, 35.16], 0.2593		3.14 [0.61, 16.32], 0.1573	
RD [95%-CI]; p-value	0.19 [-0.23, 0.61], 0.3743		0.27 [-0.12, 0.66], 0.1778		0.24 [-0.04, 0.52], 0.0971	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
EAP:n/N2 (%)	44/108 (40.7)	5/63 (7.9)	38/98 (38.8)	4/61 (6.6)	82/206 (39.8)	9/124 (7.3)
RR [95%-CI]; p-value	5.13 [2.15, 12.27], 0.0002		5.91 [2.22, 15.75], 0.0004		5.48 [2.86, 10.52], <0.0001	
OR [95%-CI]; p-value	7.98 [2.96, 21.48], <0.0001		9.03 [3.03, 26.90], <0.0001		8.45 [4.06, 17.60], <0.0001	
RD [95%-CI]; p-value	0.33 [0.21, 0.44], <0.0001		0.32 [0.21, 0.44], <0.0001		0.33 [0.24, 0.41], <0.0001	
Vist 13/ET:n/N2 (%)	44/108 (40.7)	6/63 (9.5)	45/98 (45.9)	7/61 (11.5)	89/206 (43.2)	13/124 (10.5)
RR [95%-CI]; p-value	4.28 [1.93, 9.47], 0.0003		4.00 [1.93, 8.30], 0.0002		4.12 [2.41, 7.05], <0.0001	
OR [95%-CI]; p-value	6.53 [2.59, 16.47], <0.0001		6.55 [2.71, 15.82], <0.0001		6.50 [3.43, 12.28], <0.0001	
RD [95%-CI]; p-value	0.31 [0.19, 0.43], <0.0001		0.34 [0.22, 0.47], <0.0001		0.33 [0.24, 0.41], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.

Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).

Source: Listing 14.8.1

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_1_1_1_m_pth30pct_dose.sas using SAS 9.4

Table 12.2.1.1.2.s7

Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH

ITT Population

Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2239		0.5370		0.2221	
Vist 13/ET	0.8672		0.6172		0.7069	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
EAP:n/N1 (%)	10/18 (55.6)	2/5 (40.0)	23/32 (71.9)	2/5 (40.0)	33/50 (66.0)	4/10 (40.0)
RR [95%-CI]; p-value	1.39 [0.44, 4.39], 0.5757		1.80 [0.60, 5.37], 0.2943		1.65 [0.75, 3.62], 0.2110	
OR [95%-CI]; p-value	1.88 [0.25, 14.08], 0.5379		3.83 [0.55, 26.89], 0.1568		2.91 [0.72, 11.74], 0.1227	
RD [95%-CI]; p-value	0.16 [-0.33, 0.64], 0.5312		0.32 [-0.14, 0.78], 0.1714		0.26 [-0.07, 0.59], 0.1235	
Vist 13/ET:n/N1 (%)	8/18 (44.4)	1/5 (20.0)	23/32 (71.9)	2/5 (40.0)	31/50 (62.0)	3/10 (30.0)
RR [95%-CI]; p-value	2.22 [0.36, 13.82], 0.3918		1.80 [0.60, 5.37], 0.2943		2.07 [0.78, 5.46], 0.1430	
OR [95%-CI]; p-value	3.20 [0.30, 34.59], 0.3218		3.83 [0.55, 26.89], 0.1568		3.81 [0.88, 16.53], 0.0623	
RD [95%-CI]; p-value	0.24 [-0.17, 0.66], 0.2529		0.32 [-0.14, 0.78], 0.1714		0.32 [0.01, 0.63], 0.0460	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
EAP:n/N2 (%)	77/108 (71.3)	15/63 (23.8)	67/98 (68.4)	16/61 (26.2)	144/206 (69.9)	31/124 (25.0)
RR [95%-CI]; p-value	2.99 [1.89, 4.73], <0.0001		2.61 [1.68, 4.05], <0.0001		2.80 [2.03, 3.84], <0.0001	
OR [95%-CI]; p-value	7.95 [3.89, 16.23], <0.0001		6.08 [2.98, 12.39], <0.0001		6.97 [4.21, 11.53], <0.0001	
RD [95%-CI]; p-value	0.47 [0.34, 0.61], <0.0001		0.42 [0.28, 0.57], <0.0001		0.45 [0.35, 0.55], <0.0001	
Vist 13/ET:n/N2 (%)	76/108 (70.4)	17/63 (27.0)	70/98 (71.4)	18/61 (29.5)	146/206 (70.9)	35/124 (28.2)
RR [95%-CI]; p-value	2.61 [1.71, 3.99], <0.0001		2.42 [1.61, 3.64], <0.0001		2.51 [1.87, 3.37], <0.0001	
OR [95%-CI]; p-value	6.43 [3.21, 12.85], <0.0001		5.97 [2.96, 12.07], <0.0001		6.19 [3.78, 10.13], <0.0001	
RD [95%-CI]; p-value	0.43 [0.29, 0.57], <0.0001		0.42 [0.27, 0.56], <0.0001		0.43 [0.33, 0.53], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.

Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).

Source: Listing 14.8.1

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_1_1_2_m_pth10pct_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0820		0.7680		0.1983	
Comparison Baseline vs. EAP	0.2029		0.3947		0.1615	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	19.8 (5.14)	17.5 (6.97)	21.7 (5.64)	19.8 (5.56)	21.0 (5.49)	18.6 (6.07)
Visit 13/ET						
n/N1	17/18	5/5	30/32	4/5	47/50	9/10
Mean (SD)	49.9 (19.75)	18.8 (7.98)	61.5 (19.25)	18.5 (4.43)	57.3 (20.03)	18.7 (6.26)
EAP						
n/N1	14/18	5/5	30/32	4/5	44/50	9/10
Mean (SD)	54.0 (19.43)	20.0 (8.03)	61.7 (19.83)	16.9 (5.33)	59.2 (19.81)	18.6 (6.74)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	30.3 (3.96)	2.2 (7.35)	39.8 (3.18)	-3.8 (8.70)	35.2 (2.56)	-0.9 (5.66)
95% CI	[22.05, 38.63]	[-13.20, 17.56]	[33.31, 46.27]	[-21.59, 13.92]	[30.09, 40.37]	[-12.30, 10.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	28.16		43.63		36.16	
95% CI	[10.61, 45.70]		[24.73, 62.53]		[23.69, 48.63]	
p-value	0.0033		<0.0001		<0.0001	
Hedges' g	1.74		2.48		2.17	
95% CI	[0.65, 2.83]		[1.30, 3.65]		[1.36, 2.97]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	34.4 (3.96)	3.5 (6.66)	39.9 (3.23)	-1.6 (8.92)	37.4 (2.69)	1.1 (5.65)
95% CI	[26.02, 42.81]	[-10.62, 17.63]	[33.28, 46.46]	[-19.78, 16.61]	[31.96, 42.78]	[-10.26, 12.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	30.91		41.46		36.27	
95% CI	[14.41, 47.40]		[22.06, 60.85]		[23.69, 48.86]	
p-value	0.0011		0.0001		<0.0001	
Hedges' g	2.06		2.36		2.26	
95% CI	[0.88, 3.23]		[1.19, 3.52]		[1.44, 3.09]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	20.0 (5.05)	19.3 (5.46)	19.2 (5.35)	19.3 (5.74)	19.6 (5.20)	19.3 (5.58)
Visit 13/ET						
n/N2	106/108	62/63	94/98	56/61	200/206	118/124
Mean (SD)	69.8 (23.56)	17.3 (6.01)	70.3 (23.86)	20.0 (6.94)	70.0 (23.64)	18.6 (6.59)
EAP						
n/N2	104/108	59/63	94/98	57/61	198/206	116/124
Mean (SD)	68.8 (22.10)	17.5 (6.13)	68.4 (21.75)	19.6 (6.59)	68.6 (21.88)	18.5 (6.42)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.8 (1.81)	-2.1 (2.37)	51.1 (1.96)	0.5 (2.54)	50.5 (1.33)	-0.8 (1.73)
95% CI	[46.21, 53.36]	[-6.79, 2.56]	[47.28, 55.02]	[-4.55, 5.49]	[47.86, 53.09]	[-4.24, 2.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.90		50.68		51.31	
95% CI	[46.01, 57.79]		[44.34, 57.02]		[47.02, 55.60]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.78		2.67		2.73	
95% CI	[2.35, 3.21]		[2.22, 3.11]		[2.42, 3.05]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	48.9 (1.73)	-2.0 (2.30)	49.4 (1.74)	0.3 (2.24)	49.1 (1.23)	-0.9 (1.60)
95% CI	[45.49, 52.32]	[-6.58, 2.50]	[45.94, 52.83]	[-4.16, 4.70]	[46.71, 51.55]	[-4.01, 2.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.94		49.11		49.99	
95% CI	[45.26, 56.62]		[43.50, 54.73]		[46.01, 53.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.87		2.90		2.90	
95% CI	[2.43, 3.32]		[2.44, 3.36]		[2.57, 3.22]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.1.1.s7
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0384		0.9281		0.4237	
Vist 13/ET	0.4323		0.9753		0.8666	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
EAP:n/N1 (%)	13/18 (72.2)	1/5 (20.0)	29/32 (90.6)	0/5 (0.0)	42/50 (84.0)	1/10 (10.0)
RR [95%-CI]; p-value	3.61 [0.61, 21.33], 0.1565		9.97 [0.71, 140.42], 0.0884		8.40 [1.30, 54.14], 0.0252	
OR [95%-CI]; p-value	10.40 [0.92, 117.18], 0.0343		96.67 [4.18, 2235.00], <0.0001		47.25 [5.24, 426.43], <0.0001	
RD [95%-CI]; p-value	0.52 [0.12, 0.93], 0.0119		0.82 [0.55, 1.00], <0.0001		0.74 [0.53, 0.95], <0.0001	
Vist 13/ET:n/N1 (%)	14/18 (77.8)	0/5 (0.0)	29/32 (90.6)	0/5 (0.0)	43/50 (86.0)	0/10 (0.0)
RR [95%-CI]; p-value	8.56 [0.60, 121.62], 0.1130		9.97 [0.71, 140.42], 0.0884		18.06 [1.20, 270.70], 0.0362	
OR [95%-CI]; p-value	35.00 [1.56, 786.49], 0.0037		96.67 [4.18, 2235.00], <0.0001		122.86 [6.43, 2348.37], <0.0001	
RD [95%-CI]; p-value	0.69 [0.38, 0.99], <0.0001		0.82 [0.55, 1.00], <0.0001		0.81 [0.65, 0.97], <0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
EAP:n/N2 (%)	100/108 (92.6)	1/63 (1.6)	91/98 (92.9)	5/61 (8.2)	191/206 (92.7)	6/124 (4.8)
RR [95%-CI]; p-value	58.33 [8.34, 407.99], <0.0001		11.33 [4.88, 26.28], <0.0001		19.16 [8.77, 41.86], <0.0001	
OR [95%-CI]; p-value	775.00 [94.63, 6346.90], <0.0001		145.60 [44.08, 480.97], <0.0001		250.42 [94.54, 663.36], <0.0001	
RD [95%-CI]; p-value	0.91 [0.85, 0.97], <0.0001		0.85 [0.76, 0.93], <0.0001		0.88 [0.83, 0.93], <0.0001	
Vist 13/ET:n/N2 (%)	97/108 (89.8)	2/63 (3.2)	92/98 (93.9)	6/61 (9.8)	189/206 (91.7)	8/124 (6.5)
RR [95%-CI]; p-value	28.29 [7.22, 110.81], <0.0001		9.54 [4.46, 20.44], <0.0001		14.22 [7.27, 27.83], <0.0001	
OR [95%-CI]; p-value	268.95 [57.64, 1254.94], <0.0001		140.56 [43.20, 457.36], <0.0001		161.21 [67.43, 385.38], <0.0001	
RD [95%-CI]; p-value	0.87 [0.79, 0.94], <0.0001		0.84 [0.75, 0.93], <0.0001		0.85 [0.80, 0.91], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_1_1_m_25d30_dose.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4507		0.6994		0.3302	
Comparison Baseline vs. EAP	0.1890		0.4377		0.0769	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	159.5 (49.19)	133.2 (43.35)	146.4 (61.95)	145.3 (28.16)	153.2 (55.38)	138.7 (36.90)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	118.1 (45.55)	118.4 (38.66)	123.4 (135.49)	173.1 (78.69)	120.9 (101.88)	143.0 (64.61)
EAP						
n/N1	17/23	11/11	20/21	8/9	37/44	19/20
Mean (SD)	114.4 (50.40)	116.3 (41.44)	133.4 (128.28)	171.3 (59.47)	124.7 (99.53)	139.5 (55.73)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-38.4 (9.76)	-29.2 (13.00)	-23.2 (17.71)	28.3 (27.05)	-35.2 (11.71)	7.2 (16.67)
95% CI	[-58.43, -18.37]	[-55.87, -2.52]	[-59.49, 13.18]	[-27.20, 83.81]	[-58.71, -11.77]	[-26.19, 40.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-9.21		-51.46		-42.45	
95% CI	[-43.33, 24.92]		[-117.81, 14.88]		[-83.49, -1.40]	
p-value	0.5844		0.1231		0.0429	
Hedges' g	-0.58		-0.56		-0.52	
95% CI	[-1.31, 0.16]		[-1.33, 0.21]		[-1.06, 0.02]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-41.5 (10.81)	-28.0 (13.57)	-15.9 (16.67)	27.5 (26.36)	-32.2 (11.30)	5.0 (15.95)
95% CI	[-63.74, -19.21]	[-55.93, -0.04]	[-50.18, 18.47]	[-26.82, 81.75]	[-54.92, -9.54]	[-27.02, 37.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-13.49		-43.32		-37.23	
95% CI	[-49.95, 22.98]		[-107.56, 20.92]		[-76.69, 2.23]	
p-value	0.4534		0.1771		0.0639	
Hedges' g	-0.58		-0.50		-0.46	
95% CI	[-1.34, 0.17]		[-1.31, 0.30]		[-1.01, 0.10]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	144.4 (57.10)	143.8 (46.75)	147.8 (64.83)	157.0 (66.62)	146.1 (61.07)	150.5 (57.86)
Visit 13/ET						
n/N2	110/118	57/61	111/123	54/63	221/241	111/124
Mean (SD)	113.5 (64.39)	154.5 (67.99)	114.8 (80.16)	169.4 (84.74)	114.2 (72.58)	161.7 (76.61)
EAP						
n/N2	100/118	53/61	104/123	53/63	204/241	106/124
Mean (SD)	108.7 (51.25)	152.3 (67.72)	109.2 (61.80)	154.9 (65.93)	109.0 (56.74)	153.6 (66.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.8 (4.71)	13.3 (6.55)	-29.7 (5.04)	9.4 (7.24)	-30.5 (3.45)	11.8 (4.88)
95% CI	[-40.12, -21.51]	[0.39, 26.24]	[-39.66, -19.77]	[-4.86, 23.74]	[-37.28, -23.69]	[2.24, 21.43]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.13		-39.16		-42.32	
95% CI	[-60.06, -28.20]		[-56.63, -21.69]		[-54.09, -30.56]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.89		-0.73		-0.81	
95% CI	[-1.22, -0.56]		[-1.06, -0.39]		[-1.05, -0.57]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.5 (3.98)	13.2 (5.46)	-32.7 (3.61)	2.0 (5.06)	-32.5 (2.68)	7.5 (3.71)
95% CI	[-40.36, -24.64]	[2.44, 24.04]	[-39.78, -25.53]	[-8.05, 11.96]	[-37.82, -27.28]	[0.22, 14.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.74		-34.61		-40.08	
95% CI	[-59.10, -32.39]		[-46.92, -22.30]		[-49.09, -31.07]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.14		-0.85		-1.00	
95% CI	[-1.50, -0.79]		[-1.19, -0.51]		[-1.25, -0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.1.1.1.s8
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0182		0.6402		0.2245	
Vist 13/ET	0.3477		0.4785		0.8636	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
EAP:n/N1 (%)	6/23 (26.1)	3/11 (27.3)	9/21 (42.9)	0/9 (0.0)	15/44 (34.1)	3/20 (15.0)
RR [95%-CI]; p-value	0.96 [0.29, 3.13], 0.9414		8.14 [0.52, 126.45], 0.1340		2.27 [0.74, 6.97], 0.1513	
OR [95%-CI]; p-value	0.94 [0.19, 4.76], 0.9416		13.50 [0.69, 264.73], 0.0379		2.93 [0.74, 11.61], 0.1154	
RD [95%-CI]; p-value	-0.01 [-0.33, 0.31], 0.9418		0.38 [0.12, 0.63], 0.0038		0.19 [-0.02, 0.40], 0.0748	
Vist 13/ET:n/N1 (%)	9/23 (39.1)	2/11 (18.2)	10/21 (47.6)	0/9 (0.0)	19/44 (43.2)	2/20 (10.0)
RR [95%-CI]; p-value	2.15 [0.56, 8.33], 0.2670		9.05 [0.59, 139.41], 0.1145		4.32 [1.11, 16.79], 0.0347	
OR [95%-CI]; p-value	2.89 [0.50, 16.58], 0.2219		16.36 [0.84, 320.15], 0.0226		6.84 [1.41, 33.14], 0.0088	
RD [95%-CI]; p-value	0.21 [-0.09, 0.51], 0.1752		0.42 [0.17, 0.68], 0.0012		0.33 [0.14, 0.53], 0.0009	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
EAP:n/N2 (%)	40/118 (33.9)	3/61 (4.9)	40/123 (32.5)	5/63 (7.9)	80/241 (33.2)	8/124 (6.5)
RR [95%-CI]; p-value	6.89 [2.22, 21.38], 0.0008		4.10 [1.70, 9.87], 0.0017		5.15 [2.57, 10.30], <0.0001	
OR [95%-CI]; p-value	9.91 [2.92, 33.63], <0.0001		5.59 [2.08, 15.02], 0.0002		7.20 [3.35, 15.48], <0.0001	
RD [95%-CI]; p-value	0.29 [0.19, 0.39], <0.0001		0.25 [0.14, 0.35], <0.0001		0.27 [0.19, 0.34], <0.0001	
Vist 13/ET:n/N2 (%)	45/118 (38.1)	5/61 (8.2)	51/123 (41.5)	8/63 (12.7)	96/241 (39.8)	13/124 (10.5)
RR [95%-CI]; p-value	4.65 [1.95, 11.11], 0.0005		3.27 [1.65, 6.45], 0.0007		3.80 [2.22, 6.50], <0.0001	
OR [95%-CI]; p-value	6.90 [2.57, 18.53], <0.0001		4.87 [2.14, 11.10], <0.0001		5.65 [3.01, 10.61], <0.0001	
RD [95%-CI]; p-value	0.30 [0.19, 0.41], <0.0001		0.29 [0.17, 0.41], <0.0001		0.29 [0.21, 0.38], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_1_1_1_m_pth30pct_vitd.sas using SAS 9.4

Table 12.2.1.1.2.s8
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2090		0.7585		0.5104	
Vist 13/ET	0.0438		0.9697		0.1730	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
EAP:n/N1 (%)	13/23 (56.5)	4/11 (36.4)	14/21 (66.7)	2/9 (22.2)	27/44 (61.4)	6/20 (30.0)
RR [95%-CI]; p-value	1.55 [0.66, 3.67], 0.3148		3.00 [0.85, 10.57], 0.0872		2.05 [1.01, 4.16], 0.0480	
OR [95%-CI]; p-value	2.28 [0.52, 9.99], 0.2714		7.00 [1.14, 42.97], 0.0253		3.71 [1.19, 11.50], 0.0200	
RD [95%-CI]; p-value	0.20 [-0.15, 0.55], 0.2577		0.44 [0.11, 0.78], 0.0100		0.31 [0.07, 0.56], 0.0128	
Vist 13/ET:n/N1 (%)	12/23 (52.2)	5/11 (45.5)	17/21 (81.0)	3/9 (33.3)	29/44 (65.9)	8/20 (40.0)
RR [95%-CI]; p-value	1.15 [0.54, 2.45], 0.7209		2.43 [0.94, 6.26], 0.0663		1.65 [0.93, 2.93], 0.0900	
OR [95%-CI]; p-value	1.31 [0.31, 5.53], 0.7139		8.50 [1.46, 49.54], 0.0112		2.90 [0.97, 8.63], 0.0517	
RD [95%-CI]; p-value	0.07 [-0.29, 0.43], 0.7131		0.48 [0.13, 0.83], 0.0078		0.26 [0.00, 0.52], 0.0476	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
EAP:n/N2 (%)	74/118 (62.7)	13/61 (21.3)	76/123 (61.8)	16/63 (25.4)	150/241 (62.2)	29/124 (23.4)
RR [95%-CI]; p-value	2.94 [1.78, 4.86], <0.0001		2.43 [1.56, 3.80], <0.0001		2.66 [1.91, 3.71], <0.0001	
OR [95%-CI]; p-value	6.21 [3.03, 12.73], <0.0001		4.75 [2.42, 9.32], <0.0001		5.40 [3.31, 8.82], <0.0001	
RD [95%-CI]; p-value	0.41 [0.28, 0.55], <0.0001		0.36 [0.23, 0.50], <0.0001		0.39 [0.29, 0.48], <0.0001	
Vist 13/ET:n/N2 (%)	78/118 (66.1)	14/61 (23.0)	79/123 (64.2)	17/63 (27.0)	157/241 (65.1)	31/124 (25.0)
RR [95%-CI]; p-value	2.88 [1.79, 4.64], <0.0001		2.38 [1.55, 3.65], <0.0001		2.61 [1.89, 3.58], <0.0001	
OR [95%-CI]; p-value	6.55 [3.22, 13.29], <0.0001		4.86 [2.49, 9.47], <0.0001		5.61 [3.45, 9.11], <0.0001	
RD [95%-CI]; p-value	0.43 [0.30, 0.57], <0.0001		0.37 [0.23, 0.51], <0.0001		0.40 [0.30, 0.50], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_1_1_2_m_pth10pct_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8392		0.5143		0.6359	
Comparison Baseline vs. EAP	0.2275		0.5435		0.1642	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	21.7 (5.12)	18.5 (4.57)	20.7 (4.91)	23.7 (4.18)	21.2 (4.99)	20.9 (5.05)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	64.5 (20.49)	21.2 (7.31)	68.1 (20.53)	26.9 (4.26)	66.4 (20.33)	23.8 (6.65)
EAP						
n/N1	17/23	11/11	20/21	8/9	37/44	19/20
Mean (SD)	65.1 (13.25)	21.6 (6.99)	66.4 (17.66)	26.4 (3.47)	65.8 (15.59)	23.6 (6.13)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	43.3 (4.05)	1.2 (5.41)	47.5 (3.77)	2.9 (5.86)	45.0 (2.70)	2.9 (3.84)
95% CI	[35.00, 51.61]	[-9.87, 12.33]	[39.77, 55.23]	[-9.08, 14.97]	[39.58, 50.41]	[-4.79, 10.58]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.08		44.56		42.10	
95% CI	[27.82, 56.34]		[29.99, 59.12]		[32.69, 51.50]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.25		2.58		2.48	
95% CI	[1.33, 3.17]		[1.57, 3.58]		[1.79, 3.17]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	43.7 (2.77)	2.2 (3.49)	46.0 (3.13)	1.9 (5.04)	44.4 (2.09)	2.9 (2.93)
95% CI	[37.96, 49.38]	[-5.01, 9.36]	[39.57, 52.48]	[-8.49, 12.26]	[40.20, 48.57]	[-2.97, 8.81]
Diff in LS-Mean [ER-Calcifediol - Placebo]	41.50		44.14		41.46	
95% CI	[32.05, 50.94]		[31.73, 56.55]		[34.24, 48.69]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.48		3.04		3.32	
95% CI	[2.31, 4.65]		[1.91, 4.17]		[2.50, 4.15]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	19.9 (5.04)	19.4 (5.60)	19.5 (5.66)	18.7 (5.42)	19.7 (5.36)	19.1 (5.50)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	65.2 (25.33)	16.8 (5.75)	65.2 (25.32)	18.7 (6.34)	65.2 (25.27)	17.7 (6.09)
EAP						
n/N2	101/118	53/61	104/123	53/63	205/241	106/124
Mean (SD)	67.4 (23.46)	16.8 (5.82)	66.8 (22.14)	18.4 (6.22)	67.1 (22.75)	17.6 (6.05)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.5 (1.92)	-2.6 (2.70)	45.8 (1.98)	-0.5 (2.86)	45.6 (1.38)	-1.6 (1.96)
95% CI	[41.65, 49.25]	[-7.92, 2.73]	[41.92, 49.72]	[-6.18, 5.11]	[42.93, 48.34]	[-5.43, 2.29]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.05		46.35		47.20	
95% CI	[41.51, 54.59]		[39.49, 53.21]		[42.49, 51.92]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.36		2.22		2.30	
95% CI	[1.95, 2.76]		[1.81, 2.62]		[2.01, 2.59]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.9 (1.85)	-2.6 (2.56)	47.4 (1.75)	-0.4 (2.45)	47.6 (1.27)	-1.5 (1.77)
95% CI	[44.22, 51.55]	[-7.66, 2.45]	[43.96, 50.88]	[-5.22, 4.48]	[45.14, 50.15]	[-4.95, 2.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.49		47.79		49.11	
95% CI	[44.25, 56.74]		[41.82, 53.75]		[44.82, 53.40]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.70		2.66		2.70	
95% CI	[2.26, 3.15]		[2.22, 3.11]		[2.38, 3.01]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.1.1.s8
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0391		0.0874		0.0038	
Vist 13/ET	0.0406		0.0137		0.0009	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
EAP:n/N1 (%)	17/23 (73.9)	2/11 (18.2)	19/21 (90.5)	2/9 (22.2)	36/44 (81.8)	4/20 (20.0)
RR [95%-CI]; p-value	4.07 [1.13, 14.58], 0.0313		4.07 [1.19, 13.93], 0.0253		4.09 [1.68, 9.94], 0.0019	
OR [95%-CI]; p-value	12.75 [2.12, 76.57], 0.0022		33.25 [3.90, 283.45], 0.0002		18.00 [4.73, 68.53], <0.0001	
RD [95%-CI]; p-value	0.56 [0.27, 0.85], 0.0002		0.68 [0.38, 0.98], <0.0001		0.62 [0.41, 0.83], <0.0001	
Vist 13/ET:n/N1 (%)	18/23 (78.3)	2/11 (18.2)	20/21 (95.2)	3/9 (33.3)	38/44 (86.4)	5/20 (25.0)
RR [95%-CI]; p-value	4.30 [1.21, 15.36], 0.0245		2.86 [1.13, 7.23], 0.0267		3.45 [1.60, 7.45], 0.0016	
OR [95%-CI]; p-value	16.20 [2.61, 100.45], 0.0009		40.00 [3.49, 458.98], 0.0002		19.00 [5.03, 71.75], <0.0001	
RD [95%-CI]; p-value	0.60 [0.32, 0.88], <0.0001		0.62 [0.30, 0.94], 0.0002		0.61 [0.40, 0.83], <0.0001	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
EAP:n/N2 (%)	96/118 (81.4)	0/61 (0.0)	101/123 (82.1)	3/63 (4.8)	197/241 (81.7)	3/124 (2.4)
RR [95%-CI]; p-value	100.07 [6.32, 1584.01], 0.0011		17.24 [5.70, 52.19], <0.0001		33.79 [11.03, 103.49], <0.0001	
OR [95%-CI]; p-value	532.36 [31.69, 8944.25], <0.0001		91.82 [26.36, 319.79], <0.0001		180.58 [54.87, 594.33], <0.0001	
RD [95%-CI]; p-value	0.81 [0.73, 0.88], <0.0001		0.77 [0.69, 0.86], <0.0001		0.79 [0.74, 0.85], <0.0001	
Vist 13/ET:n/N2 (%)	99/118 (83.9)	0/61 (0.0)	103/123 (83.7)	3/63 (4.8)	202/241 (83.8)	3/124 (2.4)
RR [95%-CI]; p-value	103.19 [6.52, 1633.15], 0.0010		17.59 [5.81, 53.20], <0.0001		34.64 [11.31, 106.09], <0.0001	
OR [95%-CI]; p-value	635.68 [37.66, 10730.10], <0.0001		103.00 [29.38, 361.14], <0.0001		208.91 [63.19, 690.63], <0.0001	
RD [95%-CI]; p-value	0.83 [0.76, 0.90], <0.0001		0.79 [0.71, 0.87], <0.0001		0.81 [0.76, 0.87], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_1_1_m_25d30_vitd.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6914		0.1928		0.4282	
Comparison Baseline vs. EAP	0.4637		0.0814		0.4060	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	149.7 (58.01)	143.8 (50.79)	161.8 (74.90)	161.2 (63.22)	155.8 (67.14)	152.0 (57.30)
Visit 13/ET						
n/N1	63/68	38/40	65/70	29/36	128/138	67/76
Mean (SD)	118.7 (66.92)	155.2 (69.67)	134.0 (115.53)	177.4 (83.13)	126.5 (94.72)	164.8 (76.00)
EAP						
n/N1	59/68	36/40	61/70	30/36	120/138	66/76
Mean (SD)	108.7 (50.93)	150.5 (70.60)	128.4 (99.48)	159.4 (62.15)	118.7 (79.70)	154.5 (66.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.4 (6.28)	11.7 (8.09)	-28.0 (8.89)	8.8 (13.31)	-30.0 (5.45)	10.8 (7.60)
95% CI	[-43.87, -18.95]	[-4.35, 27.76]	[-45.66, -10.35]	[-17.62, 35.26]	[-40.75, -19.27]	[-4.15, 25.81]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.11		-36.83		-40.84	
95% CI	[-63.46, -22.77]		[-68.63, -5.02]		[-59.28, -22.40]	
p-value	<0.0001		0.0237		<0.0001	
Hedges' g	-0.87		-0.52		-0.67	
95% CI	[-1.29, -0.46]		[-0.96, -0.08]		[-0.97, -0.37]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.6 (5.55)	10.4 (7.11)	-30.1 (7.27)	-1.3 (10.36)	-33.4 (4.56)	4.7 (6.17)
95% CI	[-47.62, -25.58]	[-3.71, 24.52]	[-44.59, -15.70]	[-21.94, 19.25]	[-42.42, -24.43]	[-7.52, 16.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-47.00		-28.80		-38.08	
95% CI	[-64.93, -29.08]		[-53.95, -3.65]		[-53.22, -22.94]	
p-value	<0.0001		0.0253		<0.0001	
Hedges' g	-1.11		-0.50		-0.77	
95% CI	[-1.55, -0.67]		[-0.94, -0.06]		[-1.08, -0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	144.2 (54.34)	140.2 (40.22)	134.2 (48.98)	149.9 (63.34)	139.1 (51.77)	145.4 (53.55)
Visit 13/ET						
n/N2	66/73	30/32	67/74	34/36	133/147	64/68
Mean (SD)	109.9 (56.77)	140.3 (59.46)	98.9 (52.26)	163.5 (84.15)	104.3 (54.62)	152.6 (73.97)
EAP						
n/N2	58/73	28/32	63/74	31/36	121/147	59/68
Mean (SD)	110.4 (51.41)	140.5 (58.18)	98.3 (38.95)	154.8 (68.39)	104.1 (45.56)	148.0 (63.61)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-33.7 (6.03)	2.5 (8.95)	-29.0 (5.66)	14.3 (8.01)	-32.2 (4.17)	10.3 (6.03)
95% CI	[-45.62, -21.69]	[-15.30, 20.24]	[-40.24, -17.78]	[-1.54, 30.23]	[-40.46, -24.01]	[-1.58, 22.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-36.13		-43.36		-42.54	
95% CI	[-57.59, -14.67]		[-63.02, -23.70]		[-57.01, -28.07]	
p-value	0.0012		<0.0001		<0.0001	
Hedges' g	-0.75		-0.93		-0.84	
95% CI	[-1.19, -0.31]		[-1.35, -0.50]		[-1.15, -0.53]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.2 (5.34)	3.3 (7.69)	-29.4 (4.36)	11.0 (6.25)	-31.1 (3.42)	7.9 (4.90)
95% CI	[-42.84, -21.60]	[-12.00, 18.61]	[-38.03, -20.72]	[-1.46, 23.39]	[-37.85, -24.36]	[-1.78, 17.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.53		-40.34		-39.00	
95% CI	[-54.18, -16.88]		[-55.62, -25.06]		[-50.80, -27.20]	
p-value	0.0003		<0.0001		<0.0001	
Hedges' g	-0.87		-1.07		-0.96	
95% CI	[-1.33, -0.40]		[-1.52, -0.61]		[-1.29, -0.64]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.1.1.1.s9
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.6413		0.1080		0.2217	
Vist 13/ET	0.4421		0.3884		0.9280	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
EAP:n/N1 (%)	24/68 (35.3)	3/40 (7.5)	23/70 (32.9)	5/36 (13.9)	47/138 (34.1)	8/76 (10.5)
RR [95%-CI]; p-value	4.71 [1.51, 14.64], 0.0075		2.37 [0.98, 5.70], 0.0550		3.24 [1.61, 6.49], 0.0009	
OR [95%-CI]; p-value	6.73 [1.88, 24.13], 0.0013		3.03 [1.04, 8.83], 0.0359		4.39 [1.95, 9.90], 0.0002	
RD [95%-CI]; p-value	0.28 [0.14, 0.42], <0.0001		0.19 [0.03, 0.35], 0.0184		0.24 [0.13, 0.34], <0.0001	
Vist 13/ET:n/N1 (%)	27/68 (39.7)	3/40 (7.5)	28/70 (40.0)	5/36 (13.9)	55/138 (39.9)	8/76 (10.5)
RR [95%-CI]; p-value	5.29 [1.72, 16.34], 0.0038		2.88 [1.22, 6.82], 0.0162		3.79 [1.91, 7.52], 0.0001	
OR [95%-CI]; p-value	8.12 [2.27, 29.01], 0.0003		4.13 [1.43, 11.91], 0.0060		5.63 [2.51, 12.64], <0.0001	
RD [95%-CI]; p-value	0.32 [0.18, 0.46], <0.0001		0.26 [0.10, 0.42], 0.0015		0.29 [0.19, 0.40], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
EAP:n/N2 (%)	22/73 (30.1)	3/32 (9.4)	26/74 (35.1)	0/36 (0.0)	48/147 (32.7)	3/68 (4.4)
RR [95%-CI]; p-value	3.21 [1.04, 9.98], 0.0433		25.65 [1.61, 409.36], 0.0217		7.40 [2.39, 22.92], 0.0005	
OR [95%-CI]; p-value	4.17 [1.15, 15.14], 0.0215		39.00 [2.30, 661.87], <0.0001		10.51 [3.14, 35.15], <0.0001	
RD [95%-CI]; p-value	0.21 [0.06, 0.35], 0.0053		0.34 [0.22, 0.45], <0.0001		0.28 [0.19, 0.37], <0.0001	
Vist 13/ET:n/N2 (%)	27/73 (37.0)	4/32 (12.5)	33/74 (44.6)	3/36 (8.3)	60/147 (40.8)	7/68 (10.3)
RR [95%-CI]; p-value	2.96 [1.13, 7.76], 0.0275		5.35 [1.76, 16.28], 0.0031		3.97 [1.91, 8.21], 0.0002	
OR [95%-CI]; p-value	4.11 [1.30, 12.98], 0.0113		8.85 [2.49, 31.45], 0.0001		6.01 [2.57, 14.04], <0.0001	
RD [95%-CI]; p-value	0.24 [0.09, 0.40], 0.0026		0.36 [0.22, 0.51], <0.0001		0.31 [0.20, 0.41], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_1_1_1_m_pth30pct_bl25d.sas using SAS 9.4

Table 12.2.1.1.2.s9
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.6538		0.8554		0.8487	
Vist 13/ET	0.5203		0.7435		0.4886	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
EAP:n/N1 (%)	44/68 (64.7)	9/40 (22.5)	47/70 (67.1)	10/36 (27.8)	91/138 (65.9)	19/76 (25.0)
RR [95%-CI]; p-value	2.88 [1.58, 5.25], 0.0006		2.42 [1.39, 4.20], 0.0017		2.64 [1.75, 3.96], <0.0001	
OR [95%-CI]; p-value	6.31 [2.58, 15.43], <0.0001		5.31 [2.20, 12.85], 0.0001		5.81 [3.10, 10.88], <0.0001	
RD [95%-CI]; p-value	0.42 [0.25, 0.59], <0.0001		0.39 [0.21, 0.58], <0.0001		0.41 [0.28, 0.53], <0.0001	
Vist 13/ET:n/N1 (%)	42/68 (61.8)	9/40 (22.5)	45/70 (64.3)	9/36 (25.0)	87/138 (63.0)	18/76 (23.7)
RR [95%-CI]; p-value	2.75 [1.50, 5.03], 0.0011		2.57 [1.42, 4.65], 0.0018		2.66 [1.74, 4.06], <0.0001	
OR [95%-CI]; p-value	5.56 [2.29, 13.53], <0.0001		5.40 [2.20, 13.27], 0.0001		5.50 [2.92, 10.34], <0.0001	
RD [95%-CI]; p-value	0.39 [0.22, 0.57], <0.0001		0.39 [0.21, 0.57], <0.0001		0.39 [0.27, 0.52], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
EAP:n/N2 (%)	43/73 (58.9)	8/32 (25.0)	43/74 (58.1)	8/36 (22.2)	86/147 (58.5)	16/68 (23.5)
RR [95%-CI]; p-value	2.36 [1.25, 4.42], 0.0077		2.61 [1.38, 4.96], 0.0033		2.49 [1.59, 3.90], <0.0001	
OR [95%-CI]; p-value	4.30 [1.70, 10.86], 0.0014		4.85 [1.95, 12.08], 0.0004		4.58 [2.39, 8.77], <0.0001	
RD [95%-CI]; p-value	0.34 [0.15, 0.53], 0.0004		0.36 [0.18, 0.54], <0.0001		0.35 [0.22, 0.48], <0.0001	
Vist 13/ET:n/N2 (%)	48/73 (65.8)	10/32 (31.3)	51/74 (68.9)	11/36 (30.6)	99/147 (67.3)	21/68 (30.9)
RR [95%-CI]; p-value	2.10 [1.23, 3.61], 0.0069		2.26 [1.35, 3.78], 0.0020		2.18 [1.50, 3.17], <0.0001	
OR [95%-CI]; p-value	4.22 [1.73, 10.29], 0.0011		5.04 [2.13, 11.95], 0.0001		4.62 [2.49, 8.57], <0.0001	
RD [95%-CI]; p-value	0.35 [0.15, 0.54], 0.0005		0.38 [0.20, 0.57], <0.0001		0.36 [0.23, 0.50], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_1_1_2_m_pth10pct_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4799		0.0193		0.0338	
Comparison Baseline vs. EAP	0.0849		0.1986		0.0341	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	15.7 (2.57)	15.3 (3.08)	14.9 (3.23)	15.0 (3.42)	15.3 (2.94)	15.1 (3.23)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	60.1 (25.41)	14.7 (4.91)	60.9 (27.92)	16.3 (6.12)	60.5 (26.60)	15.4 (5.47)
EAP						
n/N1	60/68	36/40	61/70	30/36	121/138	66/76
Mean (SD)	62.6 (24.64)	14.6 (4.99)	61.1 (22.05)	15.9 (5.42)	61.9 (23.28)	15.2 (5.19)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.5 (2.54)	-0.5 (3.31)	45.9 (2.93)	1.3 (4.46)	45.2 (1.93)	0.4 (2.73)
95% CI	[39.49, 49.59]	[-7.06, 6.05]	[40.11, 51.75]	[-7.60, 10.14]	[41.43, 49.04]	[-5.01, 5.76]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.05		44.66		44.86	
95% CI	[36.76, 53.34]		[34.05, 55.27]		[38.27, 51.46]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.21		1.89		2.06	
95% CI	[1.71, 2.71]		[1.37, 2.40]		[1.70, 2.42]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.1 (2.52)	-0.5 (3.26)	46.1 (2.35)	1.1 (3.35)	46.6 (1.72)	0.3 (2.34)
95% CI	[42.07, 52.10]	[-6.97, 5.98]	[41.46, 50.78]	[-5.60, 7.71]	[43.22, 50.01]	[-4.35, 4.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.58		45.07		46.35	
95% CI	[39.38, 55.77]		[36.94, 53.19]		[40.61, 52.08]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.43		2.45		2.46	
95% CI	[1.90, 2.97]		[1.88, 3.01]		[2.07, 2.85]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	24.4 (2.61)	24.2 (3.10)	24.1 (2.99)	23.8 (3.17)	24.3 (2.80)	24.0 (3.12)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	69.9 (23.03)	21.1 (5.78)	70.3 (19.94)	22.8 (5.77)	70.1 (21.46)	22.0 (5.79)
EAP						
n/N2	58/73	28/32	63/74	31/36	121/147	59/68
Mean (SD)	71.6 (18.62)	21.5 (5.57)	72.2 (19.43)	22.9 (5.56)	71.9 (18.97)	22.3 (5.56)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.5 (2.39)	-3.3 (3.57)	46.3 (2.04)	-1.2 (2.86)	45.9 (1.56)	-2.2 (2.27)
95% CI	[40.72, 50.20]	[-10.37, 3.81]	[42.22, 50.31]	[-6.84, 4.53]	[42.78, 48.95]	[-6.69, 2.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.74		47.41		48.09	
95% CI	[40.21, 57.27]		[40.43, 54.40]		[42.66, 53.52]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.48		2.80		2.64	
95% CI	[1.92, 3.03]		[2.23, 3.36]		[2.24, 3.03]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.2 (2.06)	-2.9 (2.97)	48.1 (2.05)	-1.0 (2.93)	47.7 (1.45)	-2.0 (2.08)
95% CI	[43.12, 51.33]	[-8.82, 3.00]	[44.07, 52.22]	[-6.81, 4.82]	[44.83, 50.56]	[-6.06, 2.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.13		49.14		49.65	
95% CI	[42.94, 57.33]		[42.03, 56.24]		[44.64, 54.66]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.17		2.99		3.10	
95% CI	[2.52, 3.82]		[2.38, 3.59]		[2.65, 3.55]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.1.1.s9
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.8630		0.2094		0.2098	
Vist 13/ET	0.3256		0.1479		0.0602	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
EAP:n/N1 (%)	55/68 (80.9)	1/40 (2.5)	58/70 (82.9)	1/36 (2.8)	113/138 (81.9)	2/76 (2.6)
RR [95%-CI]; p-value	32.35 [4.66, 224.86], 0.0004		29.83 [4.31, 206.63], 0.0006		31.12 [7.91, 122.43], <0.0001	
OR [95%-CI]; p-value	165.00 [20.72, 1314.05], <0.0001		169.17 [21.08, 1357.73], <0.0001		167.24 [38.46, 727.22], <0.0001	
RD [95%-CI]; p-value	0.78 [0.68, 0.89], <0.0001		0.80 [0.70, 0.90], <0.0001		0.79 [0.72, 0.87], <0.0001	
Vist 13/ET:n/N1 (%)	54/68 (79.4)	0/40 (0.0)	58/70 (82.9)	1/36 (2.8)	112/138 (81.2)	1/76 (1.3)
RR [95%-CI]; p-value	64.32 [4.08, 1013.56], 0.0031		29.83 [4.31, 206.63], 0.0006		61.68 [8.79, 432.97], <0.0001	
OR [95%-CI]; p-value	308.57 [17.84, 5336.37], <0.0001		169.17 [21.08, 1357.73], <0.0001		323.08 [42.92, 2432.04], <0.0001	
RD [95%-CI]; p-value	0.78 [0.68, 0.88], <0.0001		0.80 [0.70, 0.90], <0.0001		0.80 [0.73, 0.87], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
EAP:n/N2 (%)	58/73 (79.5)	1/32 (3.1)	62/74 (83.8)	4/36 (11.1)	120/147 (81.6)	5/68 (7.4)
RR [95%-CI]; p-value	25.42 [3.68, 175.62], 0.0010		7.54 [2.98, 19.10], <0.0001		11.10 [4.76, 25.90], <0.0001	
OR [95%-CI]; p-value	119.87 [15.12, 950.57], <0.0001		41.33 [12.33, 138.52], <0.0001		56.00 [20.56, 152.49], <0.0001	
RD [95%-CI]; p-value	0.76 [0.65, 0.87], <0.0001		0.73 [0.59, 0.86], <0.0001		0.74 [0.65, 0.83], <0.0001	
Vist 13/ET:n/N2 (%)	63/73 (86.3)	2/32 (6.3)	65/74 (87.8)	5/36 (13.9)	128/147 (87.1)	7/68 (10.3)
RR [95%-CI]; p-value	13.81 [3.60, 53.00], 0.0001		6.32 [2.79, 14.33], <0.0001		8.46 [4.18, 17.11], <0.0001	
OR [95%-CI]; p-value	94.50 [19.48, 458.43], <0.0001		44.78 [13.84, 144.84], <0.0001		58.71 [23.43, 147.12], <0.0001	
RD [95%-CI]; p-value	0.80 [0.69, 0.92], <0.0001		0.74 [0.60, 0.87], <0.0001		0.77 [0.68, 0.86], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_1_1_m_25d30_bl25d.sas using SAS 9.4

Nachberechnungsdokument Subgruppenanalyse - Wirksamkeitsendpunkte (PP-Population)

Folgende Daten werden für die PP-Population

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einem 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1743		0.1781		0.0503	
Comparison Baseline vs. EAP	0.6457		0.0333		0.0566	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	147.1 (52.84)	134.4 (40.44)	159.0 (73.62)	165.2 (72.95)	152.3 (62.73)	149.3 (59.87)
Visit 13/ET						
n/N1	51/51	28/28	39/40	25/26	90/91	53/54
Mean (SD)	119.1 (62.78)	142.9 (58.99)	120.9 (109.46)	169.8 (84.55)	119.9 (85.62)	155.6 (72.74)
EAP						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	113.6 (49.12)	145.5 (61.37)	128.1 (100.34)	157.6 (74.90)	120.0 (75.87)	151.3 (67.84)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-26.4 (7.43)	5.6 (10.05)	-38.5 (12.33)	5.2 (15.40)	-32.7 (6.90)	6.3 (8.92)
95% CI	[-41.24, -11.65]	[-14.44, 25.59]	[-63.15, -13.85]	[-25.59, 35.99]	[-46.33, -19.05]	[-11.31, 23.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-32.02		-43.70		-39.02	
95% CI	[-57.00, -7.04]		[-83.15, -4.24]		[-61.32, -16.72]	
p-value	0.0127		0.0305		0.0007	
Hedges' g	-0.65		-0.55		-0.59	
95% CI	[-1.12, -0.19]		[-1.06, -0.05]		[-0.94, -0.25]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.0 (6.07)	8.3 (8.21)	-31.0 (9.55)	-7.4 (11.84)	-31.9 (5.51)	1.5 (7.10)
95% CI	[-44.07, -19.91]	[-8.06, 24.63]	[-50.12, -11.96]	[-31.06, 16.27]	[-42.79, -21.02]	[-12.54, 15.54]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.27		-23.65		-33.41	
95% CI	[-60.67, -19.88]		[-54.06, 6.76]		[-51.17, -15.64]	
p-value	0.0002		0.1252		0.0003	
Hedges' g	-0.96		-0.38		-0.65	
95% CI	[-1.44, -0.48]		[-0.88, 0.11]		[-0.99, -0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	142.3 (51.38)	138.9 (42.58)	134.8 (54.49)	145.3 (44.52)	138.1 (53.07)	142.1 (43.35)
Visit 13/ET						
n/N2	63/64	33/34	78/79	33/34	141/143	66/68
Mean (SD)	108.5 (60.95)	153.7 (73.08)	105.8 (76.01)	163.8 (69.84)	107.0 (69.46)	158.7 (71.11)
EAP						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	106.2 (53.29)	147.4 (70.76)	106.9 (62.66)	158.6 (57.09)	106.5 (58.45)	153.0 (64.06)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-33.5 (5.86)	17.6 (8.11)	-28.9 (5.26)	17.0 (8.10)	-31.4 (3.94)	17.7 (5.72)
95% CI	[-45.18, -21.90]	[1.50, 33.69]	[-39.37, -18.52]	[0.91, 33.03]	[-39.21, -23.68]	[6.42, 28.99]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-51.13		-45.92		-49.15	
95% CI	[-71.02, -31.25]		[-65.10, -26.74]		[-62.85, -35.46]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.10		-1.01		-1.06	
95% CI	[-1.55, -0.65]		[-1.43, -0.58]		[-1.37, -0.75]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.0 (4.98)	8.3 (6.83)	-28.1 (4.25)	13.9 (6.49)	-32.1 (3.25)	11.1 (4.68)
95% CI	[-45.93, -26.17]	[-5.28, 21.84]	[-36.56, -19.73]	[1.03, 26.73]	[-38.49, -25.69]	[1.87, 20.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.33		-42.02		-43.19	
95% CI	[-61.11, -27.55]		[-57.42, -26.63]		[-54.43, -31.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.11		-1.09		-1.10	
95% CI	[-1.55, -0.67]		[-1.51, -0.66]		[-1.40, -0.79]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.1.1.1.s1.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4787		0.0534		0.1302	
Vist 13/ET	0.5997		0.1129		0.1144	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
EAP:n/N1 (%)	16/51 (31.4)	1/28 (3.6)	13/40 (32.5)	5/26 (19.2)	29/91 (31.9)	6/54 (11.1)
RR [95%-CI]; p-value	8.78 [1.23, 62.80], 0.0304		1.69 [0.68, 4.18], 0.2561		2.87 [1.27, 6.46], 0.0110	
OR [95%-CI]; p-value	12.34 [1.54, 98.97], 0.0040		2.02 [0.62, 6.57], 0.2369		3.74 [1.44, 9.74], 0.0047	
RD [95%-CI]; p-value	0.28 [0.13, 0.42], 0.0002		0.13 [-0.08, 0.34], 0.2151		0.21 [0.08, 0.33], 0.0014	
Vist 13/ET:n/N1 (%)	19/51 (37.3)	3/28 (10.7)	18/40 (45.0)	5/26 (19.2)	37/91 (40.7)	8/54 (14.8)
RR [95%-CI]; p-value	3.48 [1.13, 10.73], 0.0302		2.34 [0.99, 5.52], 0.0524		2.74 [1.38, 5.45], 0.0039	
OR [95%-CI]; p-value	4.95 [1.31, 18.62], 0.0118		3.44 [1.08, 10.93], 0.0318		3.94 [1.67, 9.31], 0.0011	
RD [95%-CI]; p-value	0.27 [0.09, 0.44], 0.0030		0.26 [0.04, 0.47], 0.0195		0.26 [0.12, 0.40], 0.0003	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
EAP:n/N2 (%)	30/64 (46.9)	4/34 (11.8)	34/79 (43.0)	0/34 (0.0)	64/143 (44.8)	4/68 (5.9)
RR [95%-CI]; p-value	3.98 [1.53, 10.37], 0.0046		29.70 [1.87, 470.75], 0.0162		7.61 [2.89, 20.03], <0.0001	
OR [95%-CI]; p-value	6.62 [2.09, 20.96], 0.0005		51.38 [3.04, 868.37], <0.0001		12.96 [4.48, 37.51], <0.0001	
RD [95%-CI]; p-value	0.35 [0.19, 0.51], <0.0001		0.42 [0.30, 0.53], <0.0001		0.39 [0.29, 0.49], <0.0001	
Vist 13/ET:n/N2 (%)	30/64 (46.9)	3/34 (8.8)	40/79 (50.6)	2/34 (5.9)	70/143 (49.0)	5/68 (7.4)
RR [95%-CI]; p-value	5.31 [1.75, 16.14], 0.0032		8.61 [2.20, 33.61], 0.0020		6.66 [2.82, 15.73], <0.0001	
OR [95%-CI]; p-value	9.12 [2.53, 32.88], 0.0001		16.41 [3.68, 73.19], <0.0001		12.08 [4.59, 31.80], <0.0001	
RD [95%-CI]; p-value	0.38 [0.23, 0.54], <0.0001		0.45 [0.31, 0.58], <0.0001		0.42 [0.31, 0.52], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_1_1_1_m_pth30pct_age_pp.sas using SAS 9.4

Table 12.2.1.1.2.s1.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2862		0.0762		0.0436	
Vist 13/ET	0.3236		0.3911		0.1795	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
EAP:n/N1 (%)	37/51 (72.5)	9/28 (32.1)	30/40 (75.0)	11/26 (42.3)	67/91 (73.6)	20/54 (37.0)
RR [95%-CI]; p-value	2.26 [1.28, 3.97], 0.0047		1.77 [1.09, 2.87], 0.0202		1.99 [1.37, 2.87], 0.0003	
OR [95%-CI]; p-value	5.58 [2.05, 15.22], 0.0005		4.09 [1.42, 11.77], 0.0075		4.75 [2.30, 9.78], <0.0001	
RD [95%-CI]; p-value	0.40 [0.19, 0.62], 0.0002		0.33 [0.09, 0.56], 0.0059		0.37 [0.21, 0.52], <0.0001	
Vist 13/ET:n/N1 (%)	32/51 (62.7)	8/28 (28.6)	32/40 (80.0)	10/26 (38.5)	64/91 (70.3)	18/54 (33.3)
RR [95%-CI]; p-value	2.20 [1.18, 4.09], 0.0133		2.08 [1.25, 3.46], 0.0049		2.11 [1.41, 3.15], 0.0003	
OR [95%-CI]; p-value	4.21 [1.55, 11.41], 0.0037		6.40 [2.12, 19.35], 0.0006		4.74 [2.30, 9.77], <0.0001	
RD [95%-CI]; p-value	0.34 [0.13, 0.56], 0.0017		0.42 [0.19, 0.64], 0.0003		0.37 [0.21, 0.53], <0.0001	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
EAP:n/N2 (%)	48/64 (75.0)	7/34 (20.6)	55/79 (69.6)	6/34 (17.6)	103/143 (72.0)	13/68 (19.1)
RR [95%-CI]; p-value	3.64 [1.85, 7.16], 0.0002		3.95 [1.88, 8.27], 0.0003		3.77 [2.29, 6.21], <0.0001	
OR [95%-CI]; p-value	11.57 [4.23, 31.63], <0.0001		10.69 [3.92, 29.18], <0.0001		10.89 [5.38, 22.07], <0.0001	
RD [95%-CI]; p-value	0.54 [0.37, 0.72], <0.0001		0.52 [0.36, 0.68], <0.0001		0.53 [0.41, 0.65], <0.0001	
Vist 13/ET:n/N2 (%)	46/64 (71.9)	7/34 (20.6)	55/79 (69.6)	8/34 (23.5)	101/143 (70.6)	15/68 (22.1)
RR [95%-CI]; p-value	3.49 [1.77, 6.88], 0.0003		2.96 [1.59, 5.52], 0.0006		3.20 [2.02, 5.07], <0.0001	
OR [95%-CI]; p-value	9.86 [3.65, 26.63], <0.0001		7.45 [2.95, 18.81], <0.0001		8.50 [4.32, 16.72], <0.0001	
RD [95%-CI]; p-value	0.51 [0.34, 0.69], <0.0001		0.46 [0.29, 0.64], <0.0001		0.49 [0.36, 0.61], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_1_1_2_m_pth10pct_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4664		0.1545		0.1327	
Comparison Baseline vs. EAP	0.0567		0.1400		0.0146	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	18.7 (4.97)	19.7 (6.40)	17.4 (5.24)	18.1 (6.48)	18.2 (5.10)	18.9 (6.43)
Visit 13/ET						
n/N1	51/51	28/28	39/40	25/26	90/91	53/54
Mean (SD)	65.7 (25.28)	16.6 (6.42)	64.0 (25.45)	18.8 (6.98)	64.9 (25.23)	17.6 (6.71)
EAP						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	65.4 (25.79)	17.2 (6.09)	60.5 (21.76)	18.6 (6.77)	63.3 (24.10)	17.9 (6.40)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.9 (2.86)	-2.9 (3.86)	46.5 (3.26)	0.7 (4.08)	46.7 (2.16)	-1.1 (2.80)
95% CI	[41.19, 52.57]	[-10.60, 4.77]	[40.03, 53.07]	[-7.46, 8.85]	[42.43, 50.98]	[-6.68, 4.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.80		45.85		47.85	
95% CI	[40.23, 59.38]		[35.38, 56.32]		[40.85, 54.86]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.44		2.25		2.38	
95% CI	[1.85, 3.04]		[1.62, 2.89]		[1.94, 2.82]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.6 (2.94)	-2.2 (3.97)	43.0 (2.74)	0.7 (3.41)	44.7 (2.05)	-0.8 (2.64)
95% CI	[40.70, 52.41]	[-10.13, 5.69]	[37.50, 48.47]	[-6.14, 7.47]	[40.70, 48.78]	[-6.02, 4.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.77		42.32		45.54	
95% CI	[38.92, 58.63]		[33.57, 51.06]		[38.94, 52.15]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.32		2.42		2.37	
95% CI	[1.74, 2.91]		[1.78, 3.06]		[1.94, 2.80]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	20.7 (5.12)	18.9 (5.07)	20.7 (5.40)	20.2 (4.78)	20.7 (5.25)	19.5 (4.94)
Visit 13/ET						
n/N2	64/64	33/34	78/79	32/34	142/143	65/68
Mean (SD)	69.4 (22.72)	18.0 (6.26)	71.8 (20.70)	20.9 (6.83)	70.8 (21.59)	19.5 (6.66)
EAP						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	67.9 (19.59)	18.1 (6.48)	70.7 (19.71)	20.2 (6.37)	69.5 (19.64)	19.2 (6.47)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.6 (2.26)	-0.7 (3.16)	51.0 (1.99)	0.3 (3.11)	49.9 (1.50)	-0.3 (2.21)
95% CI	[44.12, 53.10]	[-7.00, 5.55]	[47.09, 54.97]	[-5.86, 6.46]	[46.93, 52.84]	[-4.69, 4.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.33		50.73		50.22	
95% CI	[41.57, 57.09]		[43.42, 58.04]		[44.95, 55.50]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.75		2.87		2.83	
95% CI	[2.18, 3.32]		[2.31, 3.42]		[2.43, 3.23]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.1 (1.91)	-0.5 (2.63)	50.0 (1.83)	0.0 (2.79)	48.6 (1.33)	-0.3 (1.92)
95% CI	[43.28, 50.87]	[-5.77, 4.69]	[46.36, 53.62]	[-5.52, 5.54]	[45.95, 51.19]	[-4.11, 3.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.61		49.98		48.90	
95% CI	[41.11, 54.12]		[43.36, 56.59]		[44.29, 53.51]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.14		3.06		3.12	
95% CI	[2.54, 3.74]		[2.50, 3.63]		[2.70, 3.53]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.1.1.s1.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4494		0.9103		0.4260	
Vist 13/ET	0.8864		0.6292		0.7158	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
EAP:n/N1 (%)	48/51 (94.1)	0/28 (0.0)	38/40 (95.0)	2/26 (7.7)	86/91 (94.5)	2/54 (3.7)
RR [95%-CI]; p-value	53.65 [3.44, 837.71], 0.0045		12.35 [3.26, 46.86], 0.0002		25.52 [6.54, 99.51], <0.0001	
OR [95%-CI]; p-value	896.00 [43.29, 18543.89], <0.0001		228.00 [30.08, 1728.20], <0.0001		447.20 [83.72, 2388.89], <0.0001	
RD [95%-CI]; p-value	0.92 [0.84, 1.00], <0.0001		0.87 [0.75, 1.00], <0.0001		0.91 [0.84, 0.98], <0.0001	
Vist 13/ET:n/N1 (%)	46/51 (90.2)	1/28 (3.6)	38/40 (95.0)	2/26 (7.7)	84/91 (92.3)	3/54 (5.6)
RR [95%-CI]; p-value	25.25 [3.68, 173.43], 0.0010		12.35 [3.26, 46.86], 0.0002		16.62 [5.52, 49.98], <0.0001	
OR [95%-CI]; p-value	248.40 [27.55, 2239.54], <0.0001		228.00 [30.08, 1728.20], <0.0001		204.00 [50.48, 824.40], <0.0001	
RD [95%-CI]; p-value	0.87 [0.76, 0.97], <0.0001		0.87 [0.75, 1.00], <0.0001		0.87 [0.79, 0.95], <0.0001	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
EAP:n/N2 (%)	62/64 (96.9)	2/34 (5.9)	78/79 (98.7)	3/34 (8.8)	140/143 (97.9)	5/68 (7.4)
RR [95%-CI]; p-value	16.47 [4.29, 63.23], <0.0001		11.19 [3.80, 32.98], <0.0001		13.31 [5.73, 30.97], <0.0001	
OR [95%-CI]; p-value	496.00 [66.73, 3686.50], <0.0001		806.00 [80.72, 8048.13], <0.0001		588.00 [136.29, 2536.75], <0.0001	
RD [95%-CI]; p-value	0.91 [0.82, 1.00], <0.0001		0.90 [0.80, 1.00], <0.0001		0.91 [0.84, 0.97], <0.0001	
Vist 13/ET:n/N2 (%)	58/64 (90.6)	1/34 (2.9)	77/79 (97.5)	4/34 (11.8)	135/143 (94.4)	5/68 (7.4)
RR [95%-CI]; p-value	30.81 [4.46, 212.82], 0.0005		8.28 [3.30, 20.81], <0.0001		12.84 [5.52, 29.88], <0.0001	
OR [95%-CI]; p-value	319.00 [36.80, 2765.29], <0.0001		288.75 [50.23, 1660.00], <0.0001		212.63 [66.88, 676.01], <0.0001	
RD [95%-CI]; p-value	0.88 [0.79, 0.97], <0.0001		0.86 [0.74, 0.97], <0.0001		0.87 [0.80, 0.94], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_1_1_m_25d30_age_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6730		0.3731		0.3415	
Comparison Baseline vs. EAP	0.1980		0.0455		0.0161	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	142.8 (54.55)	136.2 (43.20)	138.9 (60.31)	153.3 (68.23)	140.9 (57.29)	145.0 (57.69)
Visit 13/ET						
n/N1	58/59	28/29	58/59	30/31	116/118	58/60
Mean (SD)	110.7 (61.77)	142.9 (56.36)	97.9 (54.43)	160.4 (89.14)	104.3 (58.32)	152.0 (75.00)
EAP						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	104.4 (46.43)	148.6 (63.26)	103.4 (53.23)	161.5 (80.39)	103.9 (49.73)	155.3 (72.30)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.4 (5.71)	9.2 (8.23)	-42.9 (6.43)	8.5 (8.96)	-37.0 (4.29)	8.5 (6.07)
95% CI	[-42.78, -20.07]	[-7.15, 25.59]	[-55.64, -30.07]	[-9.34, 26.28]	[-45.45, -28.53]	[-3.45, 20.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.64		-51.33		-45.52	
95% CI	[-60.60, -20.68]		[-73.31, -29.34]		[-60.19, -30.86]	
p-value	0.0001		<0.0001		<0.0001	
Hedges' g	-0.95		-0.92		-0.94	
95% CI	[-1.42, -0.49]		[-1.38, -0.47]		[-1.27, -0.61]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-37.9 (4.87)	11.2 (6.95)	-36.5 (5.05)	10.0 (6.98)	-37.3 (3.50)	10.9 (4.91)
95% CI	[-47.54, -28.19]	[-2.57, 25.05]	[-46.54, -26.45]	[-3.88, 23.89]	[-44.22, -30.40]	[1.18, 20.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-49.11		-46.50		-48.19	
95% CI	[-65.98, -32.23]		[-63.68, -29.32]		[-60.10, -36.28]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.27		-1.07		-1.18	
95% CI	[-1.75, -0.79]		[-1.53, -0.61]		[-1.51, -0.85]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	146.1 (49.29)	137.6 (40.31)	146.8 (64.53)	154.5 (48.06)	146.5 (57.43)	145.5 (44.56)
Visit 13/ET						
n/N2	56/56	33/33	59/60	28/29	115/116	61/62
Mean (SD)	115.9 (62.12)	153.6 (74.82)	123.6 (111.26)	172.8 (59.48)	119.9 (90.42)	162.4 (68.35)
EAP						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	114.8 (56.08)	144.7 (69.53)	124.4 (95.08)	154.6 (43.60)	119.8 (78.52)	149.3 (58.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-29.6 (7.48)	15.1 (9.76)	-22.6 (8.48)	17.8 (12.32)	-26.7 (5.72)	17.5 (7.88)
95% CI	[-44.46, -14.72]	[-4.32, 34.46]	[-39.51, -5.78]	[-6.72, 42.27]	[-37.99, -15.40]	[1.91, 33.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.66		-40.42		-44.15	
95% CI	[-69.15, -20.18]		[-70.18, -10.66]		[-63.38, -24.93]	
p-value	0.0005		0.0084		<0.0001	
Hedges' g	-0.82		-0.63		-0.72	
95% CI	[-1.26, -0.37]		[-1.09, -0.17]		[-1.03, -0.40]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-31.0 (6.05)	6.6 (7.89)	-22.3 (6.89)	-0.1 (9.92)	-26.9 (4.59)	3.6 (6.29)
95% CI	[-43.01, -18.95]	[-9.08, 22.29]	[-35.99, -8.60]	[-19.86, 19.57]	[-35.92, -17.78]	[-8.80, 16.03]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.58		-22.16		-30.47	
95% CI	[-57.39, -17.78]		[-46.18, 1.87]		[-45.84, -15.09]	
p-value	0.0003		0.0702		0.0001	
Hedges' g	-0.84		-0.42		-0.62	
95% CI	[-1.29, -0.40]		[-0.86, 0.02]		[-0.93, -0.30]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.1.1.1.s2.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2151		0.5568		0.1865	
Vist 13/ET	0.5820		0.9963		0.7167	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
EAP:n/N1 (%)	25/59 (42.4)	1/29 (3.4)	24/59 (40.7)	2/31 (6.5)	49/118 (41.5)	3/60 (5.0)
RR [95%-CI]; p-value	12.29 [1.75, 86.26], 0.0116		6.31 [1.59, 24.95], 0.0087		8.31 [2.70, 25.54], 0.0002	
OR [95%-CI]; p-value	20.59 [2.62, 161.60], 0.0002		9.94 [2.17, 45.65], 0.0007		13.49 [3.99, 45.58], <0.0001	
RD [95%-CI]; p-value	0.39 [0.25, 0.53], <0.0001		0.34 [0.19, 0.49], <0.0001		0.37 [0.26, 0.47], <0.0001	
Vist 13/ET:n/N1 (%)	24/59 (40.7)	2/29 (6.9)	32/59 (54.2)	4/31 (12.9)	56/118 (47.5)	6/60 (10.0)
RR [95%-CI]; p-value	5.90 [1.50, 23.27], 0.0113		4.20 [1.64, 10.81], 0.0029		4.75 [2.17, 10.38], <0.0001	
OR [95%-CI]; p-value	9.26 [2.01, 42.64], 0.0011		8.00 [2.49, 25.73], 0.0001		8.13 [3.25, 20.35], <0.0001	
RD [95%-CI]; p-value	0.34 [0.18, 0.49], <0.0001		0.41 [0.24, 0.59], <0.0001		0.37 [0.26, 0.49], <0.0001	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
EAP:n/N2 (%)	21/56 (37.5)	4/33 (12.1)	23/60 (38.3)	3/29 (10.3)	44/116 (37.9)	7/62 (11.3)
RR [95%-CI]; p-value	3.09 [1.16, 8.23], 0.0237		3.71 [1.21, 11.34], 0.0217		3.36 [1.61, 7.01], 0.0012	
OR [95%-CI]; p-value	4.35 [1.34, 14.12], 0.0101		5.39 [1.46, 19.84], 0.0065		4.80 [2.01, 11.48], 0.0002	
RD [95%-CI]; p-value	0.25 [0.09, 0.42], 0.0032		0.28 [0.11, 0.45], 0.0009		0.27 [0.15, 0.38], <0.0001	
Vist 13/ET:n/N2 (%)	25/56 (44.6)	4/33 (12.1)	26/60 (43.3)	3/29 (10.3)	51/116 (44.0)	7/62 (11.3)
RR [95%-CI]; p-value	3.68 [1.40, 9.66], 0.0080		4.19 [1.38, 12.71], 0.0114		3.89 [1.88, 8.06], 0.0002	
OR [95%-CI]; p-value	5.85 [1.81, 18.85], 0.0016		6.63 [1.81, 24.31], 0.0019		6.16 [2.59, 14.68], <0.0001	
RD [95%-CI]; p-value	0.33 [0.15, 0.50], 0.0002		0.33 [0.16, 0.50], 0.0001		0.33 [0.21, 0.45], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_1_1_1_m_pth30pct_sex_pp.sas using SAS 9.4

Table 12.2.1.1.2.s2.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2856		0.4932		0.7997	
Vist 13/ET	0.8161		0.7776		0.6923	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
EAP:n/N1 (%)	46/59 (78.0)	6/29 (20.7)	47/59 (79.7)	11/31 (35.5)	93/118 (78.8)	17/60 (28.3)
RR [95%-CI]; p-value	3.77 [1.82, 7.78], 0.0003		2.24 [1.37, 3.67], 0.0013		2.78 [1.84, 4.20], <0.0001	
OR [95%-CI]; p-value	13.56 [4.56, 40.31], <0.0001		7.12 [2.70, 18.81], <0.0001		9.41 [4.61, 19.22], <0.0001	
RD [95%-CI]; p-value	0.57 [0.39, 0.75], <0.0001		0.44 [0.24, 0.64], <0.0001		0.50 [0.37, 0.64], <0.0001	
Vist 13/ET:n/N1 (%)	43/59 (72.9)	8/29 (27.6)	44/59 (74.6)	10/31 (32.3)	87/118 (73.7)	18/60 (30.0)
RR [95%-CI]; p-value	2.64 [1.44, 4.86], 0.0018		2.31 [1.36, 3.93], 0.0020		2.46 [1.65, 3.67], <0.0001	
OR [95%-CI]; p-value	7.05 [2.60, 19.11], <0.0001		6.16 [2.37, 15.99], <0.0001		6.55 [3.29, 13.03], <0.0001	
RD [95%-CI]; p-value	0.45 [0.25, 0.65], <0.0001		0.42 [0.22, 0.62], <0.0001		0.44 [0.30, 0.58], <0.0001	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
EAP:n/N2 (%)	39/56 (69.6)	10/33 (30.3)	38/60 (63.3)	6/29 (20.7)	77/116 (66.4)	16/62 (25.8)
RR [95%-CI]; p-value	2.30 [1.33, 3.97], 0.0028		3.06 [1.46, 6.40], 0.0030		2.57 [1.65, 4.00], <0.0001	
OR [95%-CI]; p-value	5.28 [2.07, 13.45], 0.0003		6.62 [2.34, 18.75], 0.0002		5.68 [2.86, 11.28], <0.0001	
RD [95%-CI]; p-value	0.39 [0.20, 0.59], <0.0001		0.43 [0.24, 0.62], <0.0001		0.41 [0.27, 0.54], <0.0001	
Vist 13/ET:n/N2 (%)	35/56 (62.5)	7/33 (21.2)	43/60 (71.7)	8/29 (27.6)	78/116 (67.2)	15/62 (24.2)
RR [95%-CI]; p-value	2.95 [1.48, 5.86], 0.0021		2.60 [1.41, 4.78], 0.0022		2.78 [1.76, 4.40], <0.0001	
OR [95%-CI]; p-value	6.19 [2.29, 16.74], 0.0002		6.64 [2.47, 17.85], <0.0001		6.43 [3.20, 12.93], <0.0001	
RD [95%-CI]; p-value	0.41 [0.22, 0.60], <0.0001		0.44 [0.24, 0.64], <0.0001		0.43 [0.29, 0.57], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_1_1_2_m_pth10pct_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0876		0.2842		0.0462	
Comparison Baseline vs. EAP	0.2395		0.1711		0.0719	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	19.7 (5.08)	20.0 (5.38)	19.6 (5.31)	18.4 (4.94)	19.6 (5.18)	19.1 (5.17)
Visit 13/ET						
n/N1	59/59	28/29	58/59	29/31	117/118	57/60
Mean (SD)	74.5 (23.02)	17.9 (6.62)	73.0 (21.98)	18.3 (6.22)	73.8 (22.43)	18.1 (6.37)
EAP						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	73.3 (22.54)	18.5 (6.54)	70.4 (19.96)	18.1 (6.21)	71.9 (21.25)	18.3 (6.32)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	54.9 (2.40)	-2.2 (3.48)	53.5 (2.41)	-0.8 (3.41)	54.1 (1.71)	-1.3 (2.44)
95% CI	[50.14, 59.68]	[-9.09, 4.76]	[48.67, 58.26]	[-7.54, 6.03]	[50.73, 57.46]	[-6.09, 3.55]
Diff in LS-Mean [ER-Calcifediol - Placebo]	57.07		54.22		55.36	
95% CI	[48.66, 65.48]		[45.89, 62.54]		[49.48, 61.25]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.08		2.88		3.00	
95% CI	[2.44, 3.72]		[2.26, 3.49]		[2.56, 3.45]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	53.7 (2.35)	-1.5 (3.35)	50.9 (2.12)	-0.5 (2.93)	52.2 (1.58)	-0.9 (2.21)
95% CI	[48.99, 58.33]	[-8.17, 5.15]	[46.69, 55.11]	[-6.33, 5.30]	[49.12, 55.34]	[-5.28, 3.45]
Diff in LS-Mean [ER-Calcifediol - Placebo]	55.17		51.42		53.15	
95% CI	[47.04, 63.30]		[44.21, 58.62]		[47.78, 58.51]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.05		3.13		3.11	
95% CI	[2.42, 3.68]		[2.50, 3.76]		[2.66, 3.55]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	20.0 (5.21)	18.6 (5.93)	19.6 (5.82)	20.2 (6.24)	19.8 (5.52)	19.4 (6.08)
Visit 13/ET						
n/N2	56/56	33/33	59/60	28/29	115/116	61/62
Mean (SD)	60.6 (22.80)	16.9 (6.11)	65.5 (22.76)	21.7 (7.31)	63.1 (22.82)	19.1 (7.05)
EAP						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	60.0 (20.48)	17.1 (6.05)	64.2 (21.51)	21.0 (6.65)	62.2 (21.04)	18.9 (6.60)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	40.7 (2.41)	-1.8 (3.14)	46.0 (2.41)	1.1 (3.51)	43.3 (1.70)	-0.3 (2.34)
95% CI	[35.88, 45.45]	[-8.05, 4.44]	[41.17, 50.77]	[-5.84, 8.10]	[39.95, 46.65]	[-4.92, 4.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.47		44.84		43.60	
95% CI	[34.57, 50.37]		[36.37, 53.32]		[37.90, 49.30]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.35		2.42		2.40	
95% CI	[1.80, 2.89]		[1.85, 2.99]		[2.00, 2.79]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	40.1 (2.18)	-1.8 (2.84)	44.6 (2.22)	0.8 (3.20)	42.3 (1.55)	-0.4 (2.13)
95% CI	[35.74, 44.40]	[-7.45, 3.85]	[40.16, 49.00]	[-5.53, 7.19]	[39.22, 45.35]	[-4.61, 3.79]
Diff in LS-Mean [ER-Calcifediol - Placebo]	41.87		43.75		42.69	
95% CI	[34.72, 49.02]		[36.00, 51.50]		[37.49, 47.89]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.54		2.53		2.55	
95% CI	[1.97, 3.10]		[1.96, 3.11]		[2.15, 2.96]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.1.1.s2.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3219		0.1693		0.7129	
Vist 13/ET	0.3350		0.1083		0.4745	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
EAP:n/N1 (%)	56/59 (94.9)	2/29 (6.9)	59/59 (100.0)	1/31 (3.2)	115/118 (97.5)	3/60 (5.0)
RR [95%-CI]; p-value	13.76 [3.61, 52.48], 0.0001		30.74 [4.47, 211.41], 0.0005		19.49 [6.47, 58.75], <0.0001	
OR [95%-CI]; p-value	252.00 [39.74, 1598.17], <0.0001		3540.00 [115.44, 108550.5], <0.0001		728.33 [142.49, 3722.88], <0.0001	
RD [95%-CI]; p-value	0.88 [0.77, 0.99], <0.0001		0.96 [0.89, 1.00], <0.0001		0.92 [0.86, 0.99], <0.0001	
Vist 13/ET:n/N1 (%)	54/59 (91.5)	2/29 (6.9)	58/59 (98.3)	1/31 (3.2)	112/118 (94.9)	3/60 (5.0)
RR [95%-CI]; p-value	13.27 [3.48, 50.66], 0.0002		30.47 [4.43, 209.62], 0.0005		18.98 [6.30, 57.24], <0.0001	
OR [95%-CI]; p-value	145.80 [26.54, 801.02], <0.0001		1740.00 [105.11, 28804.16], <0.0001		354.67 [85.55, 1470.41], <0.0001	
RD [95%-CI]; p-value	0.85 [0.73, 0.96], <0.0001		0.95 [0.88, 1.00], <0.0001		0.90 [0.83, 0.97], <0.0001	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
EAP:n/N2 (%)	54/56 (96.4)	0/33 (0.0)	57/60 (95.0)	4/29 (13.8)	111/116 (95.7)	4/62 (6.5)
RR [95%-CI]; p-value	64.61 [4.12, 1012.15], 0.0030		6.89 [2.77, 17.14], <0.0001		14.83 [5.74, 38.30], <0.0001	
OR [95%-CI]; p-value	1782.00 [77.98, 40724.28], <0.0001		118.75 [24.73, 570.24], <0.0001		321.90 [83.23, 1244.92], <0.0001	
RD [95%-CI]; p-value	0.95 [0.89, 1.00], <0.0001		0.81 [0.67, 0.95], <0.0001		0.89 [0.82, 0.96], <0.0001	
Vist 13/ET:n/N2 (%)	50/56 (89.3)	0/33 (0.0)	57/60 (95.0)	5/29 (17.2)	107/116 (92.2)	5/62 (8.1)
RR [95%-CI]; p-value	59.82 [3.81, 938.14], 0.0036		5.51 [2.48, 12.26], <0.0001		11.44 [4.93, 26.55], <0.0001	
OR [95%-CI]; p-value	550.00 [29.71, 10180.25], <0.0001		91.20 [20.17, 412.31], <0.0001		135.53 [43.37, 423.56], <0.0001	
RD [95%-CI]; p-value	0.88 [0.79, 0.97], <0.0001		0.78 [0.63, 0.93], <0.0001		0.84 [0.76, 0.93], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_1_1_m_25d30_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6256		0.2292		0.2012	
Comparison Baseline vs. EAP	0.3354		0.0481		0.0266	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	145.1 (53.89)	129.2 (34.40)	150.5 (74.15)	170.1 (80.08)	147.8 (64.77)	147.4 (62.06)
Visit 13/ET						
n/N1	58/58	29/30	59/60	24/24	117/118	53/54
Mean (SD)	108.2 (64.24)	136.4 (46.72)	109.8 (89.05)	183.2 (87.74)	109.0 (77.41)	157.6 (71.64)
EAP						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	104.7 (49.64)	137.0 (53.37)	113.8 (74.32)	177.8 (85.40)	109.3 (63.30)	155.1 (71.72)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.1 (6.38)	7.4 (9.09)	-41.2 (7.22)	14.3 (11.35)	-38.7 (4.80)	12.1 (7.17)
95% CI	[-47.80, -22.41]	[-10.67, 25.47]	[-55.58, -26.85]	[-8.29, 36.89]	[-48.18, -29.22]	[-2.07, 26.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-42.51		-55.52		-50.78	
95% CI	[-64.78, -20.24]		[-82.36, -28.67]		[-67.81, -33.75]	
p-value	0.0003		<0.0001		<0.0001	
Hedges' g	-0.95		-0.96		-0.97	
95% CI	[-1.42, -0.49]		[-1.45, -0.47]		[-1.30, -0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-38.9 (4.91)	4.9 (6.85)	-37.3 (5.11)	9.3 (8.10)	-38.5 (3.54)	8.0 (5.27)
95% CI	[-48.66, -29.15]	[-8.75, 18.49]	[-47.49, -27.15]	[-6.80, 25.44]	[-45.50, -31.51]	[-2.38, 18.43]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.77		-46.64		-46.53	
95% CI	[-60.62, -26.93]		[-65.76, -27.53]		[-59.07, -33.99]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.21		-1.09		-1.16	
95% CI	[-1.69, -0.74]		[-1.59, -0.59]		[-1.51, -0.82]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	143.8 (50.17)	144.1 (46.34)	135.2 (46.82)	143.1 (36.38)	139.4 (48.48)	143.6 (41.05)
Visit 13/ET						
n/N2	56/57	32/32	58/59	34/36	114/116	66/68
Mean (SD)	118.5 (59.14)	159.9 (79.75)	112.0 (88.46)	154.5 (65.03)	115.2 (75.23)	157.1 (72.03)
EAP						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	114.3 (53.11)	155.5 (76.00)	114.1 (81.47)	145.1 (42.98)	114.2 (68.71)	150.0 (60.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-25.2 (6.84)	15.8 (9.05)	-23.2 (8.18)	10.8 (10.69)	-24.4 (5.37)	13.6 (7.06)
95% CI	[-38.76, -11.56]	[-2.17, 33.80]	[-39.47, -6.98]	[-10.47, 32.00]	[-34.99, -13.80]	[-0.31, 27.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.97		-33.98		-38.02	
95% CI	[-63.52, -18.43]		[-60.76, -7.21]		[-55.53, -20.50]	
p-value	0.0005		0.0135		<0.0001	
Hedges' g	-0.79		-0.56		-0.67	
95% CI	[-1.24, -0.35]		[-0.99, -0.13]		[-0.98, -0.36]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.5 (5.99)	11.4 (7.99)	-20.9 (6.85)	1.7 (8.78)	-25.3 (4.57)	6.8 (5.98)
95% CI	[-41.38, -17.57]	[-4.47, 27.31]	[-34.47, -7.26]	[-15.72, 19.15]	[-34.32, -16.30]	[-4.99, 18.60]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.90		-22.58		-32.11	
95% CI	[-60.75, -21.05]		[-44.73, -0.42]		[-46.96, -17.26]	
p-value	<0.0001		0.0459		<0.0001	
Hedges' g	-0.89		-0.44		-0.64	
95% CI	[-1.34, -0.44]		[-0.85, -0.02]		[-0.95, -0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.1.1.1.s3.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3995		0.8276		0.4507	
Vist 13/ET	0.3406		0.9215		0.4431	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
EAP:n/N1 (%)	28/58 (48.3)	2/30 (6.7)	26/60 (43.3)	2/24 (8.3)	54/118 (45.8)	4/54 (7.4)
RR [95%-CI]; p-value	7.24 [1.85, 28.36], 0.0045		5.20 [1.34, 20.22], 0.0173		6.18 [2.36, 16.19], 0.0002	
OR [95%-CI]; p-value	13.07 [2.85, 59.99], <0.0001		8.41 [1.81, 39.04], 0.0021		10.55 [3.58, 31.09], <0.0001	
RD [95%-CI]; p-value	0.42 [0.26, 0.57], <0.0001		0.35 [0.18, 0.52], <0.0001		0.38 [0.27, 0.50], <0.0001	
Vist 13/ET:n/N1 (%)	27/58 (46.6)	2/30 (6.7)	32/60 (53.3)	3/24 (12.5)	59/118 (50.0)	5/54 (9.3)
RR [95%-CI]; p-value	6.98 [1.78, 27.40], 0.0053		4.27 [1.44, 12.62], 0.0087		5.40 [2.30, 12.69], 0.0001	
OR [95%-CI]; p-value	12.19 [2.65, 56.00], 0.0002		8.00 [2.15, 29.70], 0.0006		9.80 [3.65, 26.33], <0.0001	
RD [95%-CI]; p-value	0.40 [0.24, 0.56], <0.0001		0.41 [0.23, 0.59], <0.0001		0.41 [0.29, 0.53], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
EAP:n/N2 (%)	18/57 (31.6)	3/32 (9.4)	21/59 (35.6)	3/36 (8.3)	39/116 (33.6)	6/68 (8.8)
RR [95%-CI]; p-value	3.37 [1.07, 10.56], 0.0373		4.27 [1.37, 13.31], 0.0123		3.81 [1.70, 8.53], 0.0011	
OR [95%-CI]; p-value	4.46 [1.20, 16.59], 0.0179		6.08 [1.66, 22.23], 0.0030		5.23 [2.08, 13.16], 0.0002	
RD [95%-CI]; p-value	0.22 [0.06, 0.38], 0.0057		0.27 [0.12, 0.42], 0.0004		0.25 [0.14, 0.36], <0.0001	
Vist 13/ET:n/N2 (%)	22/57 (38.6)	4/32 (12.5)	26/59 (44.1)	4/36 (11.1)	48/116 (41.4)	8/68 (11.8)
RR [95%-CI]; p-value	3.09 [1.17, 8.17], 0.0232		3.97 [1.51, 10.44], 0.0053		3.52 [1.77, 6.98], 0.0003	
OR [95%-CI]; p-value	4.40 [1.36, 14.26], 0.0094		6.30 [1.98, 20.10], 0.0008		5.29 [2.32, 12.08], <0.0001	
RD [95%-CI]; p-value	0.26 [0.09, 0.43], 0.0027		0.33 [0.17, 0.49], <0.0001		0.30 [0.18, 0.41], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_1_1_1_m_pth30pct_wt_pp.sas using SAS 9.4

Table 12.2.1.1.2.s3.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.9797		0.5018		0.6262	
Vist 13/ET	0.8960		0.9872		0.9880	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
EAP:n/N1 (%)	44/58 (75.9)	8/30 (26.7)	45/60 (75.0)	6/24 (25.0)	89/118 (75.4)	14/54 (25.9)
RR [95%-CI]; p-value	2.84 [1.54, 5.24], 0.0008		3.00 [1.48, 6.09], 0.0024		2.91 [1.83, 4.62], <0.0001	
OR [95%-CI]; p-value	8.64 [3.15, 23.69], <0.0001		9.00 [3.02, 26.85], <0.0001		8.77 [4.19, 18.36], <0.0001	
RD [95%-CI]; p-value	0.49 [0.30, 0.68], <0.0001		0.50 [0.30, 0.70], <0.0001		0.49 [0.35, 0.64], <0.0001	
Vist 13/ET:n/N1 (%)	42/58 (72.4)	8/30 (26.7)	43/60 (71.7)	7/24 (29.2)	85/118 (72.0)	15/54 (27.8)
RR [95%-CI]; p-value	2.72 [1.47, 5.02], 0.0014		2.46 [1.29, 4.68], 0.0062		2.59 [1.66, 4.04], <0.0001	
OR [95%-CI]; p-value	7.22 [2.67, 19.49], <0.0001		6.14 [2.16, 17.45], 0.0003		6.70 [3.26, 13.74], <0.0001	
RD [95%-CI]; p-value	0.46 [0.26, 0.65], <0.0001		0.43 [0.21, 0.64], 0.0001		0.44 [0.30, 0.59], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
EAP:n/N2 (%)	41/57 (71.9)	8/32 (25.0)	40/59 (67.8)	11/36 (30.6)	81/116 (69.8)	19/68 (27.9)
RR [95%-CI]; p-value	2.88 [1.55, 5.36], 0.0009		2.22 [1.32, 3.74], 0.0028		2.50 [1.68, 3.73], <0.0001	
OR [95%-CI]; p-value	7.69 [2.87, 20.63], <0.0001		4.78 [1.95, 11.71], 0.0004		5.97 [3.08, 11.57], <0.0001	
RD [95%-CI]; p-value	0.47 [0.28, 0.66], <0.0001		0.37 [0.18, 0.56], 0.0001		0.42 [0.28, 0.55], <0.0001	
Vist 13/ET:n/N2 (%)	36/57 (63.2)	7/32 (21.9)	44/59 (74.6)	11/36 (30.6)	80/116 (69.0)	18/68 (26.5)
RR [95%-CI]; p-value	2.89 [1.46, 5.72], 0.0024		2.44 [1.46, 4.08], 0.0007		2.61 [1.72, 3.94], <0.0001	
OR [95%-CI]; p-value	6.12 [2.26, 16.58], 0.0002		6.67 [2.66, 16.73], <0.0001		6.17 [3.17, 12.03], <0.0001	
RD [95%-CI]; p-value	0.41 [0.22, 0.60], <0.0001		0.44 [0.25, 0.63], <0.0001		0.42 [0.29, 0.56], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_1_1_2_m_pth10pct_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3994		0.7073		0.3728	
Comparison Baseline vs. EAP	0.7559		0.7958		0.7010	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	19.7 (5.18)	20.7 (5.55)	20.4 (5.67)	19.4 (6.33)	20.1 (5.42)	20.2 (5.89)
Visit 13/ET						
n/N1	58/58	29/30	59/60	23/24	117/118	52/54
Mean (SD)	71.5 (23.67)	18.6 (5.94)	74.5 (22.28)	21.0 (7.03)	73.0 (22.93)	19.7 (6.50)
EAP						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	72.0 (24.59)	18.9 (6.01)	72.0 (21.39)	20.8 (7.36)	72.0 (22.92)	19.8 (6.64)

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	51.7 (2.52)	-2.2 (3.58)	54.2 (2.49)	1.1 (3.99)	52.9 (1.77)	-0.4 (2.67)
95% CI	[46.71, 56.75]	[-9.30, 4.92]	[49.25, 59.17]	[-6.82, 9.07]	[49.43, 56.42]	[-5.71, 4.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	53.92		53.09		53.36	
95% CI	[45.20, 62.65]		[43.71, 62.46]		[47.04, 59.69]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.81		2.73		2.80	
95% CI	[2.20, 3.41]		[2.10, 3.36]		[2.36, 3.24]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	52.3 (2.61)	-1.8 (3.63)	51.7 (2.33)	1.2 (3.69)	52.0 (1.74)	-0.2 (2.59)
95% CI	[47.10, 57.46]	[-8.98, 5.45]	[47.03, 56.30]	[-6.12, 8.56]	[48.52, 55.39]	[-5.34, 4.88]
Diff in LS-Mean [ER-Calcifediol - Placebo]	54.04		50.44		52.18	
95% CI	[45.15, 62.94]		[41.75, 59.13]		[46.02, 58.35]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.72		2.77		2.78	
95% CI	[2.13, 3.32]		[2.15, 3.40]		[2.34, 3.21]	

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	20.0 (5.12)	17.9 (5.51)	18.8 (5.36)	19.2 (5.21)	19.4 (5.25)	18.5 (5.35)
Visit 13/ET						
n/N2	57/57	32/32	58/59	34/36	115/116	66/68
Mean (SD)	64.0 (23.66)	16.3 (6.54)	63.9 (21.82)	19.3 (6.87)	63.9 (22.65)	17.8 (6.83)
EAP						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	61.5 (18.88)	16.6 (6.38)	62.5 (19.40)	18.7 (5.89)	62.0 (19.07)	17.7 (6.17)

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	43.9 (2.47)	-1.4 (3.31)	44.9 (2.30)	-0.2 (3.01)	44.5 (1.68)	-0.9 (2.22)
95% CI	[39.00, 48.83]	[-7.94, 5.24]	[40.33, 49.48]	[-6.16, 5.80]	[41.20, 47.83]	[-5.32, 3.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.27		45.09		45.46	
95% CI	[36.98, 53.56]		[37.55, 52.62]		[39.95, 50.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.45		2.57		2.53	
95% CI	[1.89, 3.01]		[2.01, 3.13]		[2.13, 2.93]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	41.6 (1.99)	-1.4 (2.67)	43.6 (1.98)	-0.5 (2.54)	42.6 (1.40)	-1.0 (1.83)
95% CI	[37.65, 45.58]	[-6.72, 3.91]	[39.69, 47.56]	[-5.50, 4.57]	[39.88, 45.40]	[-4.59, 2.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	43.02		44.09		43.62	
95% CI	[36.33, 49.71]		[37.69, 50.48]		[39.06, 48.17]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.86		2.89		2.89	
95% CI	[2.26, 3.46]		[2.31, 3.47]		[2.47, 3.31]	

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.1.1.s3.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.9165		0.0961		0.1421	
Vist 13/ET	0.3548		0.6007		0.3018	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
EAP:n/N1 (%)	53/58 (91.4)	1/30 (3.3)	58/60 (96.7)	4/24 (16.7)	111/118 (94.1)	5/54 (9.3)
RR [95%-CI]; p-value	27.41 [3.98, 188.61], 0.0008		5.80 [2.37, 14.21], 0.0001		10.16 [4.40, 23.44], <0.0001	
OR [95%-CI]; p-value	307.40 [34.26, 2758.36], <0.0001		145.00 [24.65, 852.84], <0.0001		155.40 [47.00, 513.81], <0.0001	
RD [95%-CI]; p-value	0.88 [0.78, 0.98], <0.0001		0.80 [0.64, 0.96], <0.0001		0.85 [0.76, 0.94], <0.0001	
Vist 13/ET:n/N1 (%)	53/58 (91.4)	2/30 (6.7)	58/60 (96.7)	3/24 (12.5)	111/118 (94.1)	5/54 (9.3)
RR [95%-CI]; p-value	13.71 [3.58, 52.41], 0.0001		7.73 [2.68, 22.31], 0.0002		10.16 [4.40, 23.44], <0.0001	
OR [95%-CI]; p-value	148.40 [27.04, 814.41], <0.0001		203.00 [31.68, 1300.79], <0.0001		155.40 [47.00, 513.81], <0.0001	
RD [95%-CI]; p-value	0.85 [0.73, 0.96], <0.0001		0.84 [0.70, 0.98], <0.0001		0.85 [0.76, 0.94], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
EAP:n/N2 (%)	57/57 (100.0)	1/32 (3.1)	58/59 (98.3)	1/36 (2.8)	115/116 (99.1)	2/68 (2.9)
RR [95%-CI]; p-value	31.72 [4.61, 218.38], 0.0004		35.39 [5.12, 244.51], 0.0003		33.71 [8.60, 132.05], <0.0001	
OR [95%-CI]; p-value	3534.00 [115.28, 108337.3], <0.0001		2030.00 [123.03, 33495.46], <0.0001		3795.00 [337.64, 42655.08], <0.0001	
RD [95%-CI]; p-value	0.96 [0.90, 1.00], <0.0001		0.96 [0.89, 1.00], <0.0001		0.96 [0.92, 1.00], <0.0001	
Vist 13/ET:n/N2 (%)	51/57 (89.5)	0/32 (0.0)	57/59 (96.6)	3/36 (8.3)	108/116 (93.1)	3/68 (4.4)
RR [95%-CI]; p-value	58.16 [3.71, 911.42], 0.0038		11.59 [3.92, 34.29], <0.0001		21.10 [6.97, 63.87], <0.0001	
OR [95%-CI]; p-value	544.00 [29.38, 10072.87], <0.0001		313.50 [49.80, 1973.65], <0.0001		292.50 [74.92, 1142.04], <0.0001	
RD [95%-CI]; p-value	0.88 [0.79, 0.97], <0.0001		0.88 [0.78, 0.98], <0.0001		0.89 [0.82, 0.95], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_1_1_m_25d30_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7713		0.3054		0.4244	
Comparison Baseline vs. EAP	0.7884		0.5664		0.9521	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	137.4 (46.21)	129.5 (37.91)	138.8 (56.08)	143.6 (41.14)	138.2 (51.81)	136.4 (39.90)
Visit 13/ET						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	105.8 (56.48)	141.7 (57.85)	101.4 (79.96)	157.8 (63.46)	103.3 (70.42)	149.5 (60.81)
EAP						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	101.8 (49.20)	133.3 (50.35)	106.2 (75.16)	148.2 (45.88)	104.3 (64.89)	140.6 (48.50)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.0 (5.74)	11.1 (7.24)	-37.6 (6.63)	14.7 (9.67)	-34.4 (4.49)	13.0 (6.06)
95% CI	[-42.34, -19.56]	[-3.27, 25.44]	[-50.69, -24.45]	[-4.48, 33.81]	[-43.25, -25.57]	[1.09, 24.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-42.03		-52.23		-47.44	
95% CI	[-60.40, -23.67]		[-75.45, -29.02]		[-62.30, -32.58]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.92		-0.85		-0.88	
95% CI	[-1.33, -0.52]		[-1.24, -0.46]		[-1.16, -0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.9 (4.57)	2.7 (5.76)	-32.7 (5.39)	5.0 (7.87)	-34.0 (3.63)	4.1 (4.90)
95% CI	[-43.98, -25.85]	[-8.69, 14.16]	[-43.37, -22.03]	[-10.57, 20.58]	[-41.13, -26.83]	[-5.57, 13.74]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.65		-37.71		-38.07	
95% CI	[-52.26, -23.04]		[-56.60, -18.81]		[-50.08, -26.05]	
p-value	<0.0001		0.0001		<0.0001	
Hedges' g	-1.03		-0.75		-0.86	
95% CI	[-1.45, -0.62]		[-1.14, -0.36]		[-1.14, -0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	153.6 (57.58)	151.4 (44.81)	152.4 (74.83)	173.1 (80.02)	153.1 (64.94)	162.3 (65.00)
Visit 13/ET						
n/N2	49/50	20/21	34/36	19/21	83/86	39/42
Mean (SD)	123.2 (67.38)	163.2 (81.62)	134.0 (103.90)	184.1 (96.12)	127.6 (83.85)	173.4 (88.43)
EAP						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	119.4 (52.95)	172.3 (84.99)	131.8 (81.26)	176.7 (88.53)	124.6 (66.13)	174.5 (85.74)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.1 (7.95)	15.4 (12.45)	-19.3 (9.71)	7.1 (13.02)	-25.2 (6.27)	12.2 (9.01)
95% CI	[-46.00, -14.26]	[-9.41, 40.30]	[-38.84, 0.16]	[-19.07, 33.24]	[-37.60, -12.76]	[-5.65, 30.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.58		-26.43		-37.36	
95% CI	[-75.08, -16.07]		[-59.19, 6.33]		[-59.11, -15.61]	
p-value	0.0030		0.1115		0.0009	
Hedges' g	-0.83		-0.49		-0.68	
95% CI	[-1.36, -0.29]		[-1.05, 0.07]		[-1.07, -0.30]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.0 (6.71)	20.6 (10.36)	-21.0 (7.19)	4.3 (9.44)	-27.7 (4.99)	13.0 (7.05)
95% CI	[-47.42, -20.62]	[-0.05, 41.31]	[-35.45, -6.60]	[-14.60, 23.25]	[-37.59, -17.85]	[-0.99, 26.91]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-54.65		-25.35		-40.68	
95% CI	[-79.29, -30.01]		[-49.24, -1.46]		[-57.79, -23.57]	
p-value	<0.0001		0.0380		<0.0001	
Hedges' g	-1.13		-0.56		-0.88	
95% CI	[-1.66, -0.59]		[-1.10, -0.02]		[-1.26, -0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.1.1.1.s4.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4678		0.0785		0.4946	
Vist 13/ET	0.3189		0.7022		0.6023	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
EAP:n/N1 (%)	25/65 (38.5)	4/41 (9.8)	38/83 (45.8)	2/39 (5.1)	63/148 (42.6)	6/80 (7.5)
RR [95%-CI]; p-value	3.94 [1.48, 10.51], 0.0061		8.93 [2.27, 35.14], 0.0017		5.68 [2.57, 12.53], <0.0001	
OR [95%-CI]; p-value	5.78 [1.84, 18.19], 0.0012		15.62 [3.53, 69.11], <0.0001		9.14 [3.74, 22.34], <0.0001	
RD [95%-CI]; p-value	0.29 [0.14, 0.44], 0.0002		0.41 [0.28, 0.53], <0.0001		0.35 [0.25, 0.45], <0.0001	
Vist 13/ET:n/N1 (%)	26/65 (40.0)	5/41 (12.2)	47/83 (56.6)	5/39 (12.8)	73/148 (49.3)	10/80 (12.5)
RR [95%-CI]; p-value	3.28 [1.37, 7.86], 0.0077		4.42 [1.91, 10.23], 0.0005		3.95 [2.16, 7.21], <0.0001	
OR [95%-CI]; p-value	4.80 [1.66, 13.84], 0.0022		8.88 [3.16, 24.97], <0.0001		6.81 [3.26, 14.23], <0.0001	
RD [95%-CI]; p-value	0.28 [0.12, 0.43], 0.0005		0.44 [0.29, 0.59], <0.0001		0.37 [0.26, 0.48], <0.0001	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
EAP:n/N2 (%)	21/50 (42.0)	1/21 (4.8)	9/36 (25.0)	3/21 (14.3)	30/86 (34.9)	4/42 (9.5)
RR [95%-CI]; p-value	8.82 [1.27, 61.39], 0.0279		1.75 [0.53, 5.76], 0.3570		3.66 [1.38, 9.72], 0.0091	
OR [95%-CI]; p-value	14.48 [1.80, 116.56], 0.0020		2.00 [0.48, 8.41], 0.3385		5.09 [1.66, 15.62], 0.0023	
RD [95%-CI]; p-value	0.37 [0.21, 0.54], <0.0001		0.11 [-0.10, 0.31], 0.3078		0.25 [0.12, 0.39], 0.0002	
Vist 13/ET:n/N2 (%)	23/50 (46.0)	1/21 (4.8)	11/36 (30.6)	2/21 (9.5)	34/86 (39.5)	3/42 (7.1)
RR [95%-CI]; p-value	9.66 [1.39, 66.96], 0.0217		3.21 [0.79, 13.10], 0.1045		5.53 [1.80, 16.99], 0.0028	
OR [95%-CI]; p-value	17.04 [2.12, 136.91], 0.0008		4.18 [0.83, 21.13], 0.0679		8.50 [2.43, 29.71], 0.0001	
RD [95%-CI]; p-value	0.41 [0.25, 0.58], <0.0001		0.21 [0.01, 0.41], 0.0354		0.32 [0.19, 0.45], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_1_1_1_m_pth30pct_race_pp.sas using SAS 9.4

Table 12.2.1.1.2.s4.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.5223		0.1304		0.6001	
Vist 13/ET	0.5815		0.5979		0.9746	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
EAP:n/N1 (%)	50/65 (76.9)	12/41 (29.3)	66/83 (79.5)	10/39 (25.6)	116/148 (78.4)	22/80 (27.5)
RR [95%-CI]; p-value	2.63 [1.60, 4.31], 0.0001		3.10 [1.80, 5.35], <0.0001		2.85 [1.98, 4.11], <0.0001	
OR [95%-CI]; p-value	8.06 [3.32, 19.54], <0.0001		11.26 [4.60, 27.55], <0.0001		9.56 [5.10, 17.90], <0.0001	
RD [95%-CI]; p-value	0.48 [0.30, 0.65], <0.0001		0.54 [0.38, 0.70], <0.0001		0.51 [0.39, 0.63], <0.0001	
Vist 13/ET:n/N1 (%)	45/65 (69.2)	11/41 (26.8)	66/83 (79.5)	12/39 (30.8)	111/148 (75.0)	23/80 (28.8)
RR [95%-CI]; p-value	2.58 [1.52, 4.39], 0.0005		2.58 [1.59, 4.19], 0.0001		2.61 [1.82, 3.73], <0.0001	
OR [95%-CI]; p-value	6.14 [2.57, 14.63], <0.0001		8.74 [3.68, 20.73], <0.0001		7.43 [4.04, 13.69], <0.0001	
RD [95%-CI]; p-value	0.42 [0.25, 0.60], <0.0001		0.49 [0.32, 0.66], <0.0001		0.46 [0.34, 0.58], <0.0001	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
EAP:n/N2 (%)	35/50 (70.0)	4/21 (19.0)	19/36 (52.8)	7/21 (33.3)	54/86 (62.8)	11/42 (26.2)
RR [95%-CI]; p-value	3.68 [1.49, 9.04], 0.0046		1.58 [0.80, 3.12], 0.1848		2.40 [1.41, 4.09], 0.0013	
OR [95%-CI]; p-value	9.92 [2.85, 34.47], <0.0001		2.24 [0.73, 6.84], 0.1551		4.76 [2.10, 10.74], 0.0001	
RD [95%-CI]; p-value	0.51 [0.30, 0.72], <0.0001		0.19 [-0.06, 0.45], 0.1417		0.37 [0.20, 0.53], <0.0001	
Vist 13/ET:n/N2 (%)	33/50 (66.0)	4/21 (19.0)	21/36 (58.3)	6/21 (28.6)	54/86 (62.8)	10/42 (23.8)
RR [95%-CI]; p-value	3.47 [1.40, 8.56], 0.0070		2.04 [0.98, 4.24], 0.0555		2.64 [1.50, 4.64], 0.0008	
OR [95%-CI]; p-value	8.25 [2.40, 28.41], 0.0003		3.50 [1.10, 11.12], 0.0299		5.40 [2.35, 12.43], <0.0001	
RD [95%-CI]; p-value	0.47 [0.26, 0.68], <0.0001		0.30 [0.05, 0.55], 0.0204		0.39 [0.23, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_1_1_2_m_pth10pct_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0709		0.7026		0.2632	
Comparison Baseline vs. EAP	0.0488		0.8874		0.0993	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	20.7 (4.64)	19.9 (5.81)	20.3 (5.25)	20.2 (5.47)	20.5 (4.98)	20.0 (5.61)
Visit 13/ET						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	69.7 (21.49)	17.7 (6.37)	70.3 (23.56)	20.6 (7.05)	70.0 (22.60)	19.1 (6.84)
EAP						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	67.8 (19.76)	17.9 (6.27)	69.0 (21.48)	20.5 (6.71)	68.5 (20.68)	19.1 (6.58)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.1 (2.12)	-2.4 (2.68)	50.1 (2.12)	0.5 (3.09)	49.5 (1.51)	-0.9 (2.05)
95% CI	[44.85, 53.27]	[-7.71, 2.90]	[45.87, 54.25]	[-5.64, 6.59]	[46.55, 52.52]	[-4.95, 3.11]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.47		49.58		50.46	
95% CI	[44.68, 58.25]		[42.17, 57.00]		[45.44, 55.47]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.97		2.57		2.76	
95% CI	[2.41, 3.52]		[2.07, 3.06]		[2.39, 3.13]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.2 (1.95)	-2.2 (2.46)	48.8 (1.88)	0.3 (2.75)	48.0 (1.37)	-0.9 (1.85)
95% CI	[43.36, 51.11]	[-7.10, 2.66]	[45.05, 52.51]	[-5.12, 5.76]	[45.27, 50.66]	[-4.53, 2.76]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.45		48.46		48.85	
95% CI	[43.21, 55.69]		[41.87, 55.06]		[44.31, 53.38]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.09		2.82		2.96	
95% CI	[2.52, 3.66]		[2.30, 3.33]		[2.58, 3.35]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	18.7 (5.55)	18.0 (5.29)	18.2 (6.02)	17.6 (5.69)	18.5 (5.72)	17.8 (5.43)
Visit 13/ET						
n/N2	50/50	20/21	34/36	18/21	84/86	38/42
Mean (SD)	65.3 (26.65)	16.8 (6.32)	66.6 (20.12)	18.6 (6.60)	65.8 (24.09)	17.6 (6.43)
EAP						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	65.5 (25.74)	17.4 (6.42)	63.2 (19.17)	17.7 (5.95)	64.6 (23.12)	17.6 (6.12)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.5 (3.05)	-1.0 (4.83)	48.4 (2.90)	0.3 (3.99)	47.5 (2.22)	-0.6 (3.24)
95% CI	[40.42, 52.61]	[-10.61, 8.67]	[42.53, 54.19]	[-7.73, 8.29]	[43.14, 51.93]	[-6.99, 5.86]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.49		48.08		48.10	
95% CI	[36.07, 58.91]		[38.17, 57.99]		[40.32, 55.88]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.19		2.74		2.41	
95% CI	[1.56, 2.82]		[1.97, 3.52]		[1.93, 2.90]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.7 (2.97)	-0.4 (4.58)	45.2 (2.63)	-0.1 (3.44)	46.0 (2.07)	-0.3 (2.93)
95% CI	[40.81, 52.65]	[-9.57, 8.72]	[39.95, 50.48]	[-7.04, 6.75]	[41.86, 50.07]	[-6.12, 5.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.15		45.36		46.29	
95% CI	[36.25, 58.05]		[36.68, 54.04]		[39.18, 53.39]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.24		2.75		2.45	
95% CI	[1.62, 2.87]		[2.02, 3.48]		[1.98, 2.93]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.1.1.s4.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.5958		0.2547		0.3060	
Vist 13/ET	0.6753		0.3890		0.2495	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
EAP:n/N1 (%)	64/65 (98.5)	1/41 (2.4)	82/83 (98.8)	5/39 (12.8)	146/148 (98.6)	6/80 (7.5)
RR [95%-CI]; p-value	40.37 [5.82, 279.84], 0.0002		7.71 [3.40, 17.47], <0.0001		13.15 [6.09, 28.40], <0.0001	
OR [95%-CI]; p-value	2560.00 [155.70, 42090.61], <0.0001		557.60 [62.78, 4952.16], <0.0001		900.33 [177.36, 4570.26], <0.0001	
RD [95%-CI]; p-value	0.96 [0.90, 1.00], <0.0001		0.86 [0.75, 0.97], <0.0001		0.91 [0.85, 0.97], <0.0001	
Vist 13/ET:n/N1 (%)	61/65 (93.8)	2/41 (4.9)	82/83 (98.8)	5/39 (12.8)	143/148 (96.6)	7/80 (8.8)
RR [95%-CI]; p-value	19.24 [4.97, 74.44], <0.0001		7.71 [3.40, 17.47], <0.0001		11.04 [5.44, 22.42], <0.0001	
OR [95%-CI]; p-value	297.38 [51.97, 1701.54], <0.0001		557.60 [62.78, 4952.16], <0.0001		298.26 [91.49, 972.35], <0.0001	
RD [95%-CI]; p-value	0.89 [0.80, 0.98], <0.0001		0.86 [0.75, 0.97], <0.0001		0.88 [0.81, 0.95], <0.0001	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
EAP:n/N2 (%)	46/50 (92.0)	1/21 (4.8)	34/36 (94.4)	0/21 (0.0)	80/86 (93.0)	1/42 (2.4)
RR [95%-CI]; p-value	19.32 [2.85, 131.05], 0.0024		40.61 [2.62, 629.28], 0.0081		39.07 [5.63, 271.16], 0.0002	
OR [95%-CI]; p-value	230.00 [24.16, 2189.41], <0.0001		714.00 [30.71, 16601.35], <0.0001		546.67 [63.66, 4694.05], <0.0001	
RD [95%-CI]; p-value	0.87 [0.75, 0.99], <0.0001		0.92 [0.82, 1.00], <0.0001		0.91 [0.84, 0.98], <0.0001	
Vist 13/ET:n/N2 (%)	43/50 (86.0)	0/21 (0.0)	33/36 (91.7)	1/21 (4.8)	76/86 (88.4)	1/42 (2.4)
RR [95%-CI]; p-value	36.98 [2.38, 573.67], 0.0099		19.25 [2.84, 130.68], 0.0025		37.12 [5.34, 257.77], 0.0003	
OR [95%-CI]; p-value	258.00 [13.97, 4765.29], <0.0001		220.00 [21.40, 2261.89], <0.0001		311.60 [38.52, 2520.31], <0.0001	
RD [95%-CI]; p-value	0.84 [0.72, 0.95], <0.0001		0.87 [0.74, 1.00], <0.0001		0.86 [0.78, 0.94], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_1_1_m_25d30_race_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2237		0.8262		0.5806	
Comparison Baseline vs. EAP	0.0797		0.8073		0.4432	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	124.4 (39.82)	128.1 (33.64)	127.2 (34.87)	146.5 (59.64)	125.9 (37.16)	136.7 (48.08)
Visit 13/ET						
n/N1	57/58	33/33	63/65	27/29	120/123	60/62
Mean (SD)	99.3 (43.38)	137.8 (69.57)	94.8 (37.18)	142.4 (77.08)	97.0 (40.14)	139.9 (72.45)
EAP						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	95.8 (38.63)	133.4 (65.28)	98.7 (35.50)	140.3 (63.89)	97.3 (36.89)	136.6 (64.20)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-25.1 (6.44)	10.7 (8.47)	-33.0 (4.29)	-2.7 (6.60)	-29.2 (3.85)	4.5 (5.49)
95% CI	[-37.94, -12.35]	[-6.16, 27.49]	[-41.48, -24.44]	[-15.77, 10.47]	[-36.83, -21.63]	[-6.34, 15.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.81		-30.31		-33.73	
95% CI	[-56.97, -14.66]		[-46.08, -14.53]		[-47.01, -20.44]	
p-value	0.0011		0.0003		<0.0001	
Hedges' g	-0.68		-0.83		-0.75	
95% CI	[-1.12, -0.25]		[-1.29, -0.36]		[-1.07, -0.43]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.0 (5.57)	6.0 (7.38)	-29.5 (3.47)	-4.0 (5.23)	-29.4 (3.23)	1.3 (4.57)
95% CI	[-40.07, -17.94]	[-8.69, 20.65]	[-36.37, -22.59]	[-14.38, 6.42]	[-35.75, -22.98]	[-7.76, 10.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-34.98		-25.50		-30.63	
95% CI	[-53.37, -16.60]		[-38.08, -12.92]		[-41.72, -19.53]	
p-value	0.0003		0.0001		<0.0001	
Hedges' g	-0.77		-0.78		-0.78	
95% CI	[-1.21, -0.33]		[-1.23, -0.33]		[-1.09, -0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	164.8 (54.99)	147.0 (47.27)	161.8 (80.73)	160.9 (58.21)	163.3 (68.43)	154.2 (53.22)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	127.2 (73.56)	161.5 (61.85)	129.6 (121.72)	187.3 (69.45)	128.4 (99.47)	175.1 (66.66)
EAP						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	123.3 (58.90)	161.5 (65.02)	132.4 (106.10)	174.9 (62.08)	127.7 (84.92)	168.4 (63.34)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-37.1 (6.77)	16.9 (9.72)	-32.2 (10.55)	26.4 (13.92)	-34.8 (6.21)	21.9 (8.54)
95% CI	[-50.59, -23.64]	[-2.48, 36.21]	[-53.18, -11.23]	[-1.31, 54.06]	[-47.05, -22.52]	[5.02, 38.74]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-53.98		-58.58		-56.67	
95% CI	[-77.74, -30.21]		[-93.32, -23.84]		[-77.55, -35.78]	
p-value	<0.0001		0.0012		<0.0001	
Hedges' g	-1.08		-0.75		-0.88	
95% CI	[-1.56, -0.61]		[-1.21, -0.30]		[-1.21, -0.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-40.7 (5.39)	13.0 (7.59)	-29.4 (8.41)	14.0 (11.10)	-35.2 (4.95)	13.8 (6.74)
95% CI	[-51.38, -29.94]	[-2.07, 28.12]	[-46.11, -12.66]	[-8.09, 36.05]	[-44.93, -25.39]	[0.48, 27.08]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-53.69		-43.37		-48.94	
95% CI	[-72.31, -35.06]		[-71.06, -15.68]		[-65.47, -32.42]	
p-value	<0.0001		0.0025		<0.0001	
Hedges' g	-1.36		-0.70		-0.95	
95% CI	[-1.85, -0.87]		[-1.15, -0.25]		[-1.28, -0.62]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.1.1.1.s5.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2858		0.5581		0.2374	
Vist 13/ET	0.1803		0.4125		0.1276	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
EAP:n/N1 (%)	24/58 (41.4)	4/33 (12.1)	25/65 (38.5)	3/29 (10.3)	49/123 (39.8)	7/62 (11.3)
RR [95%-CI]; p-value	3.41 [1.30, 8.99], 0.0130		3.72 [1.22, 11.33], 0.0209		3.53 [1.70, 7.33], 0.0007	
OR [95%-CI]; p-value	5.12 [1.59, 16.47], 0.0036		5.42 [1.48, 19.78], 0.0059		5.20 [2.19, 12.36], <0.0001	
RD [95%-CI]; p-value	0.29 [0.12, 0.46], 0.0007		0.28 [0.12, 0.44], 0.0007		0.29 [0.17, 0.40], <0.0001	
Vist 13/ET:n/N1 (%)	25/58 (43.1)	5/33 (15.2)	28/65 (43.1)	4/29 (13.8)	53/123 (43.1)	9/62 (14.5)
RR [95%-CI]; p-value	2.84 [1.20, 6.72], 0.0172		3.12 [1.21, 8.09], 0.0190		2.97 [1.57, 5.61], 0.0008	
OR [95%-CI]; p-value	4.24 [1.43, 12.55], 0.0064		4.73 [1.48, 15.15], 0.0057		4.46 [2.02, 9.84], 0.0001	
RD [95%-CI]; p-value	0.28 [0.10, 0.46], 0.0019		0.29 [0.12, 0.47], 0.0010		0.29 [0.16, 0.41], <0.0001	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
EAP:n/N2 (%)	22/57 (38.6)	1/29 (3.4)	22/54 (40.7)	2/31 (6.5)	44/111 (39.6)	3/60 (5.0)
RR [95%-CI]; p-value	11.19 [1.59, 78.95], 0.0154		6.31 [1.59, 25.06], 0.0088		7.93 [2.57, 24.46], 0.0003	
OR [95%-CI]; p-value	17.60 [2.23, 138.74], 0.0005		9.97 [2.15, 46.14], 0.0007		12.48 [3.68, 42.34], <0.0001	
RD [95%-CI]; p-value	0.35 [0.21, 0.49], <0.0001		0.34 [0.19, 0.50], <0.0001		0.35 [0.24, 0.45], <0.0001	
Vist 13/ET:n/N2 (%)	24/57 (42.1)	1/29 (3.4)	30/54 (55.6)	3/31 (9.7)	54/111 (48.6)	4/60 (6.7)
RR [95%-CI]; p-value	12.21 [1.74, 85.81], 0.0119		5.74 [1.91, 17.27], 0.0019		7.30 [2.78, 19.17], <0.0001	
OR [95%-CI]; p-value	20.36 [2.59, 160.22], 0.0002		11.67 [3.16, 43.07], <0.0001		13.26 [4.50, 39.08], <0.0001	
RD [95%-CI]; p-value	0.39 [0.24, 0.53], <0.0001		0.46 [0.29, 0.63], <0.0001		0.42 [0.31, 0.53], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_1_1_1_m_pth30pct_ckd_pp.sas using SAS 9.4

Table 12.2.1.1.2.s5.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4172		0.4241		0.2575	
Vist 13/ET	0.2466		0.6740		0.2817	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
EAP:n/N1 (%)	43/58 (74.1)	10/33 (30.3)	48/65 (73.8)	10/29 (34.5)	91/123 (74.0)	20/62 (32.3)
RR [95%-CI]; p-value	2.45 [1.43, 4.20], 0.0011		2.14 [1.27, 3.61], 0.0043		2.29 [1.58, 3.34], <0.0001	
OR [95%-CI]; p-value	6.59 [2.56, 17.00], <0.0001		5.36 [2.09, 13.80], 0.0003		5.97 [3.06, 11.64], <0.0001	
RD [95%-CI]; p-value	0.44 [0.25, 0.63], <0.0001		0.39 [0.19, 0.60], 0.0001		0.42 [0.28, 0.56], <0.0001	
Vist 13/ET:n/N1 (%)	39/58 (67.2)	10/33 (30.3)	50/65 (76.9)	10/29 (34.5)	89/123 (72.4)	20/62 (32.3)
RR [95%-CI]; p-value	2.22 [1.28, 3.84], 0.0043		2.23 [1.33, 3.75], 0.0024		2.24 [1.54, 3.27], <0.0001	
OR [95%-CI]; p-value	4.72 [1.88, 11.88], 0.0007		6.33 [2.43, 16.52], <0.0001		5.50 [2.83, 10.67], <0.0001	
RD [95%-CI]; p-value	0.37 [0.17, 0.57], 0.0003		0.42 [0.22, 0.63], <0.0001		0.40 [0.26, 0.54], <0.0001	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
EAP:n/N2 (%)	42/57 (73.7)	6/29 (20.7)	37/54 (68.5)	7/31 (22.6)	79/111 (71.2)	13/60 (21.7)
RR [95%-CI]; p-value	3.56 [1.72, 7.38], 0.0006		3.03 [1.54, 5.97], 0.0013		3.28 [2.00, 5.39], <0.0001	
OR [95%-CI]; p-value	10.73 [3.66, 31.44], <0.0001		7.46 [2.69, 20.68], <0.0001		8.93 [4.26, 18.69], <0.0001	
RD [95%-CI]; p-value	0.53 [0.34, 0.72], <0.0001		0.46 [0.27, 0.65], <0.0001		0.50 [0.36, 0.63], <0.0001	
Vist 13/ET:n/N2 (%)	39/57 (68.4)	5/29 (17.2)	37/54 (68.5)	8/31 (25.8)	76/111 (68.5)	13/60 (21.7)
RR [95%-CI]; p-value	3.97 [1.75, 8.98], 0.0009		2.66 [1.42, 4.95], 0.0021		3.16 [1.92, 5.20], <0.0001	
OR [95%-CI]; p-value	10.40 [3.41, 31.67], <0.0001		6.26 [2.33, 16.81], 0.0001		7.85 [3.77, 16.34], <0.0001	
RD [95%-CI]; p-value	0.51 [0.33, 0.69], <0.0001		0.43 [0.23, 0.62], <0.0001		0.47 [0.33, 0.60], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_1_1_2_m_pth10pct_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6108		0.4807		0.8752	
Comparison Baseline vs. EAP	0.5063		0.6511		0.4382	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	20.6 (5.04)	19.4 (5.97)	20.0 (5.76)	19.0 (5.44)	20.3 (5.42)	19.2 (5.69)
Visit 13/ET						
n/N1	58/58	33/33	63/65	27/29	121/123	60/62
Mean (SD)	67.8 (25.15)	18.1 (6.61)	67.2 (19.61)	20.1 (6.61)	67.5 (22.34)	19.0 (6.63)
EAP						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	67.6 (23.96)	18.5 (6.73)	65.5 (20.07)	19.3 (6.11)	66.5 (21.92)	18.9 (6.41)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	47.1 (2.54)	-1.0 (3.37)	47.2 (2.08)	0.4 (3.17)	47.2 (1.64)	-0.4 (2.34)
95% CI	[42.08, 52.18]	[-7.71, 5.70]	[43.12, 51.37]	[-5.89, 6.72]	[44.01, 50.47]	[-4.99, 4.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.13		46.83		47.61	
95% CI	[39.72, 56.54]		[39.30, 54.37]		[41.97, 53.25]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.50		2.81		2.66	
95% CI	[1.94, 3.05]		[2.21, 3.42]		[2.25, 3.08]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (2.46)	-0.7 (3.27)	45.6 (2.06)	0.1 (3.08)	46.3 (1.60)	-0.3 (2.25)
95% CI	[42.07, 51.86]	[-7.22, 5.78]	[41.53, 49.71]	[-6.00, 6.25]	[43.16, 49.46]	[-4.76, 4.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.69		45.50		46.63	
95% CI	[39.53, 55.85]		[38.12, 52.87]		[41.17, 52.08]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.55		2.72		2.65	
95% CI	[1.98, 3.11]		[2.14, 3.30]		[2.24, 3.06]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	19.1 (5.16)	19.1 (5.41)	19.2 (5.31)	19.5 (5.88)	19.2 (5.21)	19.3 (5.62)
Visit 13/ET						
n/N2	57/57	28/29	54/54	30/31	111/111	58/60
Mean (SD)	67.7 (22.69)	16.6 (5.97)	71.6 (25.64)	19.9 (7.31)	69.6 (24.14)	18.3 (6.84)
EAP						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	66.0 (21.06)	16.8 (5.68)	69.4 (21.87)	19.7 (7.02)	67.7 (21.42)	18.3 (6.52)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.6 (2.48)	-2.6 (3.54)	52.3 (2.82)	0.3 (3.78)	50.5 (1.87)	-1.1 (2.59)
95% CI	[43.64, 53.52]	[-9.65, 4.44]	[46.74, 57.95]	[-7.24, 7.80]	[46.77, 54.15]	[-6.26, 3.96]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.19		52.06		51.61	
95% CI	[42.58, 59.80]		[42.68, 61.45]		[45.31, 57.91]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.71		2.51		2.62	
95% CI	[2.10, 3.32]		[1.93, 3.09]		[2.19, 3.04]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.9 (2.29)	-2.3 (3.21)	50.2 (2.33)	0.2 (3.07)	48.6 (1.63)	-1.1 (2.22)
95% CI	[42.37, 51.47]	[-8.73, 4.03]	[45.58, 54.83]	[-5.91, 6.31]	[45.33, 51.77]	[-5.44, 3.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.27		50.01		49.61	
95% CI	[41.43, 57.10]		[42.34, 57.67]		[44.17, 55.04]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.83		2.91		2.88	
95% CI	[2.22, 3.44]		[2.30, 3.53]		[2.45, 3.32]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.1.1.s5.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4081		0.2176		0.6624	
Vist 13/ET	0.9360		0.4442		0.4446	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
EAP:n/N1 (%)	55/58 (94.8)	2/33 (6.1)	64/65 (98.5)	1/29 (3.4)	119/123 (96.7)	3/62 (4.8)
RR [95%-CI]; p-value	15.65 [4.08, 60.03], <0.0001		28.55 [4.16, 195.96], 0.0006		19.99 [6.63, 60.33], <0.0001	
OR [95%-CI]; p-value	284.17 [45.02, 1793.83], <0.0001		1792.00 [108.19, 29680.50], <0.0001		585.08 [126.80, 2699.67], <0.0001	
RD [95%-CI]; p-value	0.89 [0.79, 0.99], <0.0001		0.95 [0.88, 1.00], <0.0001		0.92 [0.86, 0.98], <0.0001	
Vist 13/ET:n/N1 (%)	52/58 (89.7)	1/33 (3.0)	63/65 (96.9)	2/29 (6.9)	115/123 (93.5)	3/62 (4.8)
RR [95%-CI]; p-value	29.59 [4.29, 204.25], 0.0006		14.05 [3.69, 53.56], 0.0001		19.32 [6.40, 58.33], <0.0001	
OR [95%-CI]; p-value	277.33 [31.91, 2410.38], <0.0001		425.25 [56.91, 3177.42], <0.0001		282.71 [72.31, 1105.37], <0.0001	
RD [95%-CI]; p-value	0.87 [0.77, 0.96], <0.0001		0.90 [0.80, 1.00], <0.0001		0.89 [0.82, 0.96], <0.0001	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
EAP:n/N2 (%)	55/57 (96.5)	0/29 (0.0)	52/54 (96.3)	4/31 (12.9)	107/111 (96.4)	4/60 (6.7)
RR [95%-CI]; p-value	56.93 [3.64, 889.34], 0.0040		7.46 [2.99, 18.65], <0.0001		14.46 [5.61, 37.29], <0.0001	
OR [95%-CI]; p-value	1595.00 [69.63, 36536.80], <0.0001		175.50 [30.20, 1019.98], <0.0001		374.50 [90.24, 1554.17], <0.0001	
RD [95%-CI]; p-value	0.95 [0.88, 1.00], <0.0001		0.83 [0.71, 0.96], <0.0001		0.90 [0.83, 0.97], <0.0001	
Vist 13/ET:n/N2 (%)	52/57 (91.2)	1/29 (3.4)	52/54 (96.3)	4/31 (12.9)	104/111 (93.7)	5/60 (8.3)
RR [95%-CI]; p-value	26.46 [3.85, 181.83], 0.0009		7.46 [2.99, 18.65], <0.0001		11.24 [4.85, 26.06], <0.0001	
OR [95%-CI]; p-value	291.20 [32.41, 2616.64], <0.0001		175.50 [30.20, 1019.98], <0.0001		163.43 [49.56, 538.95], <0.0001	
RD [95%-CI]; p-value	0.88 [0.78, 0.98], <0.0001		0.83 [0.71, 0.96], <0.0001		0.85 [0.77, 0.94], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_1_1_m_25d30_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3446		0.7001		0.7611	
Comparison Baseline vs. EAP	0.0230		0.6798		0.3301	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	97.9 (9.42)	99.9 (9.86)	100.1 (9.22)	102.7 (7.61)	99.1 (9.31)	101.1 (9.00)
Visit 13/ET						
n/N1	36/36	23/23	47/48	16/16	83/84	39/39
Mean (SD)	85.3 (40.42)	112.6 (43.22)	76.7 (30.29)	113.6 (42.61)	80.5 (35.08)	113.0 (42.41)
EAP						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	84.4 (35.82)	101.8 (34.64)	80.5 (29.62)	110.0 (26.06)	82.1 (32.28)	105.2 (31.29)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-12.6 (6.79)	12.6 (8.50)	-23.2 (4.79)	10.8 (8.25)	-17.9 (4.07)	11.7 (5.99)
95% CI	[-26.16, 1.04]	[-4.43, 29.64]	[-32.80, -13.63]	[-5.70, 27.31]	[-25.94, -9.83]	[-0.17, 23.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-25.17		-34.01		-29.58	
95% CI	[-47.02, -3.32]		[-53.17, -14.86]		[-43.97, -15.20]	
p-value	0.0248		0.0007		<0.0001	
Hedges' g	-0.62		-1.03		-0.83	
95% CI	[-1.15, -0.09]		[-1.62, -0.45]		[-1.23, -0.44]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-13.3 (5.60)	1.5 (7.01)	-19.4 (3.84)	6.6 (6.68)	-16.3 (3.31)	4.1 (4.90)
95% CI	[-24.54, -2.10]	[-12.52, 15.58]	[-27.08, -11.71]	[-6.74, 19.99]	[-22.90, -9.78]	[-5.60, 13.81]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-14.85		-26.02		-20.44	
95% CI	[-32.87, 3.18]		[-41.49, -10.55]		[-32.19, -8.69]	
p-value	0.1045		0.0013		0.0008	
Hedges' g	-0.46		-1.00		-0.70	
95% CI	[-0.98, 0.07]		[-1.59, -0.42]		[-1.09, -0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	133.7 (10.99)	133.1 (12.01)	133.0 (12.77)	133.4 (11.95)	133.4 (11.79)	133.3 (11.84)
Visit 13/ET						
n/N2	41/42	22/22	36/37	22/23	77/79	44/45
Mean (SD)	102.1 (33.69)	133.5 (39.56)	113.0 (42.10)	147.1 (59.07)	107.2 (38.00)	140.3 (50.16)
EAP						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	97.4 (27.78)	137.1 (33.13)	111.1 (35.31)	142.5 (39.65)	103.8 (32.06)	139.9 (36.29)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.1 (5.60)	0.3 (7.65)	-19.3 (7.77)	12.9 (9.95)	-25.4 (4.85)	7.0 (6.40)
95% CI	[-42.28, -19.86]	[-15.01, 15.60]	[-34.88, -3.73]	[-7.03, 32.83]	[-35.03, -15.83]	[-5.67, 19.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-31.36		-32.20		-32.43	
95% CI	[-50.33, -12.40]		[-57.52, -6.89]		[-48.32, -16.53]	
p-value	0.0016		0.0136		<0.0001	
Hedges' g	-0.81		-0.70		-0.76	
95% CI	[-1.34, -0.27]		[-1.23, -0.16]		[-1.14, -0.38]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.2 (4.55)	3.8 (6.29)	-21.9 (5.68)	9.0 (7.20)	-29.1 (3.63)	6.5 (4.80)
95% CI	[-45.29, -27.08]	[-8.76, 16.40]	[-33.30, -10.55]	[-5.44, 23.41]	[-36.30, -21.94]	[-2.98, 16.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.00		-30.91		-35.63	
95% CI	[-55.53, -24.47]		[-49.28, -12.54]		[-47.54, -23.73]	
p-value	<0.0001		0.0014		<0.0001	
Hedges' g	-1.33		-0.89		-1.11	
95% CI	[-1.89, -0.77]		[-1.43, -0.35]		[-1.50, -0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	201.8 (51.09)	191.8 (31.69)	214.2 (74.73)	215.3 (58.98)	207.7 (63.35)	204.8 (49.55)
Visit 13/ET						
n/N3	37/37	16/17	34/34	20/21	71/71	36/38
Mean (SD)	152.8 (81.15)	221.5 (69.71)	155.8 (143.37)	229.9 (70.46)	154.2 (114.37)	226.1 (69.24)
EAP						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	147.5 (62.88)	219.2 (70.62)	164.5 (121.07)	212.1 (70.37)	155.6 (94.96)	215.3 (69.62)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-48.7 (10.93)	31.7 (16.68)	-58.0 (14.65)	11.6 (19.10)	-53.9 (9.12)	22.9 (12.88)
95% CI	[-70.68, -26.77]		[-87.43, -28.62]		[-71.99, -35.81]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-80.48		-69.66		-76.81	
95% CI	[-120.67, -40.28]		[-117.99, -21.32]		[-108.13, -45.50]	
p-value	0.0002		0.0056		<0.0001	
Hedges' g	-1.22		-0.80		-0.97	
95% CI	[-1.84, -0.60]		[-1.37, -0.24]		[-1.39, -0.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-53.7 (9.03)	25.9 (13.35)	-49.6 (12.05)	-3.3 (15.33)	-52.0 (7.54)	12.2 (10.36)
95% CI	[-71.80, -35.54]		[-73.78, -25.43]		[-66.99, -37.08]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-79.59		-46.33		-64.21	
95% CI	[-112.02, -47.16]		[-85.45, -7.20]		[-89.63, -38.79]	
p-value	<0.0001		0.0212		<0.0001	
Hedges' g	-1.46		-0.65		-0.98	
95% CI	[-2.09, -0.83]		[-1.20, -0.10]		[-1.39, -0.57]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.1.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3615		0.8544		0.6823	
Vist 13/ET	0.4599		0.4531		0.2335	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
EAP:n/N1 (%)	11/36 (30.6)	3/23 (13.0)	18/48 (37.5)	1/16 (6.3)	29/84 (34.5)	4/39 (10.3)
RR [95%-CI]; p-value	2.34 [0.73, 7.51], 0.1519		6.00 [0.87, 41.44], 0.0692		3.37 [1.27, 8.91], 0.0146	
OR [95%-CI]; p-value	2.93 [0.72, 11.96], 0.1231		9.00 [1.09, 74.00], 0.0178		4.61 [1.49, 14.25], 0.0047	
RD [95%-CI]; p-value	0.18 [-0.03, 0.38], 0.0924		0.31 [0.13, 0.49], 0.0007		0.24 [0.10, 0.38], 0.0006	
Vist 13/ET:n/N1 (%)	12/36 (33.3)	3/23 (13.0)	24/48 (50.0)	2/16 (12.5)	36/84 (42.9)	5/39 (12.8)
RR [95%-CI]; p-value	2.56 [0.81, 8.09], 0.1104		4.00 [1.06, 15.08], 0.0406		3.34 [1.42, 7.86], 0.0057	
OR [95%-CI]; p-value	3.33 [0.82, 13.48], 0.0809		7.00 [1.43, 34.19], 0.0082		5.10 [1.81, 14.33], 0.0010	
RD [95%-CI]; p-value	0.20 [-0.00, 0.41], 0.0542		0.38 [0.16, 0.59], 0.0006		0.30 [0.15, 0.45], <0.0001	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
EAP:n/N2 (%)	19/42 (45.2)	1/22 (4.5)	11/37 (29.7)	2/23 (8.7)	30/79 (38.0)	3/45 (6.7)
RR [95%-CI]; p-value	9.95 [1.43, 69.51], 0.0205		3.42 [0.83, 14.06], 0.0884		5.70 [1.84, 17.62], 0.0025	
OR [95%-CI]; p-value	17.35 [2.13, 141.11], 0.0009		4.44 [0.89, 22.28], 0.0545		8.57 [2.44, 30.11], 0.0001	
RD [95%-CI]; p-value	0.41 [0.23, 0.58], <0.0001		0.21 [0.02, 0.40], 0.0274		0.31 [0.18, 0.44], <0.0001	
Vist 13/ET:n/N2 (%)	19/42 (45.2)	3/22 (13.6)	11/37 (29.7)	3/23 (13.0)	30/79 (38.0)	6/45 (13.3)
RR [95%-CI]; p-value	3.32 [1.10, 10.00], 0.0331		2.28 [0.71, 7.31], 0.1660		2.85 [1.28, 6.32], 0.0100	
OR [95%-CI]; p-value	5.23 [1.34, 20.40], 0.0115		2.82 [0.69, 11.48], 0.1373		3.98 [1.51, 10.52], 0.0037	
RD [95%-CI]; p-value	0.32 [0.11, 0.52], 0.0029		0.17 [-0.03, 0.37], 0.1047		0.25 [0.10, 0.39], 0.0009	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_1_m_pth30pct_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.1.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
EAP:n/N3 (%)	16/37 (43.2)	1/17 (5.9)	18/34 (52.9)	2/21 (9.5)	34/71 (47.9)	3/38 (7.9)
RR [95%-CI]; p-value	7.35 [1.06, 51.00], 0.0435		5.56 [1.43, 21.57], 0.0131		6.07 [1.99, 18.46], 0.0015	
OR [95%-CI]; p-value	12.19 [1.46, 101.80], 0.0060		10.69 [2.15, 53.21], 0.0011		10.72 [3.02, 38.09], <0.0001	
RD [95%-CI]; p-value	0.37 [0.18, 0.57], 0.0002		0.43 [0.22, 0.64], <0.0001		0.40 [0.26, 0.54], <0.0001	
Vist 13/ET:n/N3 (%)	18/37 (48.6)	0/17 (0.0)	23/34 (67.6)	2/21 (9.5)	41/71 (57.7)	2/38 (5.3)
RR [95%-CI]; p-value	17.03 [1.09, 266.86], 0.0435		7.10 [1.86, 27.09], 0.0041		10.97 [2.81, 42.90], 0.0006	
OR [95%-CI]; p-value	32.21 [1.80, 576.81], 0.0009		19.86 [3.91, 100.83], <0.0001		24.60 [5.49, 110.22], <0.0001	
RD [95%-CI]; p-value	0.46 [0.28, 0.64], <0.0001		0.58 [0.38, 0.78], <0.0001		0.52 [0.39, 0.66], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_1_m_pth30pct_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.2.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3116		0.9619		0.5745	
Vist 13/ET	0.2436		0.3832		0.1485	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
EAP:n/N1 (%)	25/36 (69.4)	8/23 (34.8)	36/48 (75.0)	5/16 (31.3)	61/84 (72.6)	13/39 (33.3)
RR [95%-CI]; p-value	2.00 [1.10, 3.64], 0.0239		2.40 [1.14, 5.05], 0.0213		2.18 [1.37, 3.46], 0.0010	
OR [95%-CI]; p-value	4.26 [1.40, 12.97], 0.0089		6.60 [1.90, 22.87], 0.0016		5.30 [2.34, 12.05], <0.0001	
RD [95%-CI]; p-value	0.35 [0.10, 0.59], 0.0058		0.44 [0.18, 0.70], 0.0009		0.39 [0.22, 0.57], <0.0001	
Vist 13/ET:n/N1 (%)	25/36 (69.4)	6/23 (26.1)	34/48 (70.8)	6/16 (37.5)	59/84 (70.2)	12/39 (30.8)
RR [95%-CI]; p-value	2.66 [1.29, 5.48], 0.0078		1.89 [0.98, 3.65], 0.0582		2.28 [1.40, 3.73], 0.0010	
OR [95%-CI]; p-value	6.44 [2.00, 20.75], 0.0011		4.05 [1.23, 13.28], 0.0171		5.31 [2.33, 12.12], <0.0001	
RD [95%-CI]; p-value	0.43 [0.20, 0.67], 0.0003		0.33 [0.06, 0.60], 0.0155		0.39 [0.22, 0.57], <0.0001	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
EAP:n/N2 (%)	35/42 (83.3)	6/22 (27.3)	22/37 (59.5)	5/23 (21.7)	57/79 (72.2)	11/45 (24.4)
RR [95%-CI]; p-value	3.06 [1.52, 6.13], 0.0016		2.74 [1.20, 6.21], 0.0161		2.95 [1.73, 5.02], <0.0001	
OR [95%-CI]; p-value	13.33 [3.86, 46.10], <0.0001		5.28 [1.61, 17.33], 0.0043		8.01 [3.46, 18.53], <0.0001	
RD [95%-CI]; p-value	0.56 [0.34, 0.78], <0.0001		0.38 [0.15, 0.61], 0.0014		0.48 [0.32, 0.64], <0.0001	
Vist 13/ET:n/N2 (%)	30/42 (71.4)	8/22 (36.4)	23/37 (62.2)	7/23 (30.4)	53/79 (67.1)	15/45 (33.3)
RR [95%-CI]; p-value	1.96 [1.09, 3.53], 0.0237		2.04 [1.05, 3.98], 0.0359		2.01 [1.29, 3.13], 0.0019	
OR [95%-CI]; p-value	4.38 [1.46, 13.10], 0.0067		3.76 [1.24, 11.38], 0.0169		4.08 [1.87, 8.87], 0.0003	
RD [95%-CI]; p-value	0.35 [0.11, 0.59], 0.0047		0.32 [0.07, 0.56], 0.0110		0.34 [0.17, 0.51], 0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_2_m_pth10pct_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.2.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
EAP:n/N3 (%)	25/37 (67.6)	2/17 (11.8)	27/34 (79.4)	7/21 (33.3)	52/71 (73.2)	9/38 (23.7)
RR [95%-CI]; p-value	5.74 [1.53, 21.52], 0.0095		2.38 [1.27, 4.47], 0.0068		3.09 [1.72, 5.57], 0.0002	
OR [95%-CI]; p-value	15.63 [3.07, 79.59], 0.0001		7.71 [2.25, 26.41], 0.0006		8.82 [3.54, 22.00], <0.0001	
RD [95%-CI]; p-value	0.56 [0.34, 0.77], <0.0001		0.46 [0.22, 0.70], 0.0002		0.50 [0.33, 0.67], <0.0001	
Vist 13/ET:n/N3 (%)	23/37 (62.2)	1/17 (5.9)	30/34 (88.2)	5/21 (23.8)	53/71 (74.6)	6/38 (15.8)
RR [95%-CI]; p-value	10.57 [1.55, 71.94], 0.0160		3.71 [1.71, 8.04], 0.0009		4.73 [2.24, 9.98], <0.0001	
OR [95%-CI]; p-value	26.29 [3.13, 220.47], 0.0001		24.00 [5.64, 102.11], <0.0001		15.70 [5.65, 43.67], <0.0001	
RD [95%-CI]; p-value	0.56 [0.37, 0.75], <0.0001		0.64 [0.43, 0.86], <0.0001		0.59 [0.43, 0.74], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_2_m_pth10pct_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3632		0.6757		0.2671	
Comparison Baseline vs. EAP	0.9311		0.7857		0.8568	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	20.3 (5.20)	20.8 (6.16)	20.7 (5.37)	21.6 (5.44)	20.5 (5.27)	21.1 (5.82)
Visit 13/ET						
n/N1	36/36	23/23	47/48	16/16	83/84	39/39
Mean (SD)	68.8 (26.04)	18.0 (6.68)	71.2 (21.45)	20.8 (5.53)	70.1 (23.43)	19.2 (6.30)
EAP						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	66.7 (23.64)	18.7 (6.52)	70.5 (20.27)	21.1 (6.37)	68.9 (21.72)	19.7 (6.49)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.5 (3.30)	-2.8 (4.13)	50.3 (2.75)	-0.5 (4.71)	49.4 (2.14)	-1.7 (3.15)
95% CI	[41.90, 55.14]	[-11.08, 5.49]	[44.76, 55.76]	[-9.93, 8.93]	[45.14, 53.63]	[-7.94, 4.54]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.31		50.76		51.09	
95% CI	[40.71, 61.92]		[39.84, 61.68]		[43.53, 58.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.57		2.67		2.67	
95% CI	[1.87, 3.26]		[1.94, 3.40]		[2.17, 3.18]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.4 (3.03)	-2.1 (3.79)	49.8 (2.54)	-0.3 (4.40)	48.1 (1.96)	-1.2 (2.90)
95% CI	[40.37, 52.50]	[-9.69, 5.49]	[44.73, 54.89]	[-9.11, 8.50]	[44.24, 52.01]	[-6.98, 4.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.54		50.12		49.36	
95% CI	[38.82, 58.25]		[39.94, 60.30]		[42.41, 56.30]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.66		2.84		2.80	
95% CI	[1.95, 3.36]		[2.10, 3.59]		[2.29, 3.32]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	19.8 (4.72)	17.7 (5.49)	20.0 (5.87)	19.3 (5.22)	19.9 (5.26)	18.5 (5.35)
Visit 13/ET						
n/N2	42/42	22/22	36/37	22/23	78/79	44/45
Mean (SD)	69.5 (20.30)	16.2 (5.76)	62.8 (17.17)	20.5 (6.96)	66.4 (19.10)	18.3 (6.67)
EAP						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	68.8 (21.27)	16.6 (6.28)	60.5 (16.52)	19.4 (5.77)	64.9 (19.53)	18.1 (6.12)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	50.2 (2.62)	-2.3 (3.65)	43.0 (2.32)	0.9 (2.96)	46.5 (1.76)	-0.6 (2.34)
95% CI	[44.91, 55.40]	[-9.61, 4.98]	[38.34, 47.63]	[-5.08, 6.80]	[43.04, 50.03]	[-5.28, 4.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	52.47		42.12		47.17	
95% CI	[43.40, 61.54]		[34.58, 49.66]		[41.34, 53.00]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.96		2.97		2.95	
95% CI	[2.24, 3.69]		[2.22, 3.73]		[2.43, 3.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	49.6 (2.76)	-2.1 (3.84)	40.5 (2.12)	0.1 (2.69)	45.0 (1.76)	-0.8 (2.34)
95% CI	[44.07, 55.13]	[-9.78, 5.60]	[36.27, 44.75]	[-5.29, 5.47]	[41.49, 48.48]	[-5.48, 3.79]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.69		40.42		45.83	
95% CI	[42.13, 61.25]		[33.57, 47.28]		[40.00, 51.66]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.74		3.10		2.82	
95% CI	[2.04, 3.44]		[2.35, 3.86]		[2.32, 3.33]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	19.5 (5.59)	19.3 (4.90)	17.7 (5.09)	17.5 (5.84)	18.6 (5.39)	18.3 (5.44)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	64.9 (25.71)	18.1 (6.68)	73.3 (27.81)	18.8 (8.05)	68.9 (26.88)	18.5 (7.36)
EAP						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	64.6 (23.08)	17.8 (6.06)	70.1 (24.56)	18.4 (7.48)	67.3 (23.79)	18.1 (6.80)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.4 (3.42)	-1.3 (5.19)	55.7 (3.72)	0.5 (4.97)	50.5 (2.51)	-0.4 (3.58)
95% CI	[38.52, 52.25]		[48.19, 63.11]		[45.54, 55.49]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.67		55.12		50.88	
95% CI	[34.19, 59.16]		[42.65, 67.59]		[42.21, 59.56]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.23		2.50		2.35	
95% CI	[1.51, 2.94]		[1.77, 3.23]		[1.84, 2.86]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	45.1 (2.98)	-1.4 (4.39)	52.4 (3.20)	0.9 (4.07)	48.8 (2.17)	-0.3 (2.98)
95% CI	[39.17, 51.12]		[45.97, 58.80]		[44.45, 53.07]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.58		51.52		49.05	
95% CI	[35.92, 57.23]		[41.13, 61.91]		[41.73, 56.37]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.54		2.74		2.63	
95% CI	[1.80, 3.29]		[1.99, 3.48]		[2.11, 3.16]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.1.1.s6.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.9697		0.4323		0.4866	
Vist 13/ET	0.8289		0.6806		0.3890	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
EAP:n/N1 (%)	35/36 (97.2)	1/23 (4.3)	48/48 (100.0)	2/16 (12.5)	83/84 (98.8)	3/39 (7.7)
RR [95%-CI]; p-value	22.36 [3.29, 152.17], 0.0015		7.92 [2.16, 28.96], 0.0018		12.85 [4.33, 38.11], <0.0001	
OR [95%-CI]; p-value	770.00 [45.78, 12952.30], <0.0001		672.00 [28.63, 15770.54], <0.0001		996.00 [100.19, 9901.78], <0.0001	
RD [95%-CI]; p-value	0.93 [0.83, 1.00], <0.0001		0.86 [0.70, 1.00], <0.0001		0.91 [0.82, 1.00], <0.0001	
Vist 13/ET:n/N1 (%)	32/36 (88.9)	0/23 (0.0)	47/48 (97.9)	1/16 (6.3)	79/84 (94.0)	1/39 (2.6)
RR [95%-CI]; p-value	41.78 [2.69, 649.99], 0.0077		15.67 [2.35, 104.55], 0.0045		36.68 [5.30, 254.07], 0.0003	
OR [95%-CI]; p-value	368.00 [18.54, 7306.00], <0.0001		705.00 [41.52, 11971.57], <0.0001		600.40 [67.76, 5319.94], <0.0001	
RD [95%-CI]; p-value	0.87 [0.75, 0.99], <0.0001		0.92 [0.79, 1.00], <0.0001		0.91 [0.84, 0.99], <0.0001	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
EAP:n/N2 (%)	41/42 (97.6)	1/22 (4.5)	36/37 (97.3)	0/23 (0.0)	77/79 (97.5)	1/45 (2.2)
RR [95%-CI]; p-value	21.48 [3.16, 145.83], 0.0017		45.73 [2.94, 710.12], 0.0063		43.86 [6.31, 304.73], 0.0001	
OR [95%-CI]; p-value	861.00 [51.26, 14463.16], <0.0001		1656.00 [53.37, 51379.63], <0.0001		1694.00 [149.30, 19220.11], <0.0001	
RD [95%-CI]; p-value	0.93 [0.83, 1.00], <0.0001		0.95 [0.87, 1.00], <0.0001		0.95 [0.90, 1.00], <0.0001	
Vist 13/ET:n/N2 (%)	40/42 (95.2)	1/22 (4.5)	36/37 (97.3)	2/23 (8.7)	76/79 (96.2)	3/45 (6.7)
RR [95%-CI]; p-value	20.95 [3.08, 142.36], 0.0019		11.19 [2.97, 42.11], 0.0004		14.43 [4.83, 43.10], <0.0001	
OR [95%-CI]; p-value	420.00 [35.96, 4905.59], <0.0001		378.00 [32.29, 4424.62], <0.0001		354.67 [68.52, 1835.83], <0.0001	
RD [95%-CI]; p-value	0.91 [0.80, 1.00], <0.0001		0.89 [0.76, 1.00], <0.0001		0.90 [0.81, 0.98], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_1_1_m_25d30_ttlpth_pp.sas using SAS 9.4

Table 12.3.1.1.s6.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
EAP:n/N3 (%)	34/37 (91.9)	0/17 (0.0)	32/34 (94.1)	3/21 (14.3)	66/71 (93.0)	3/38 (7.9)
RR [95%-CI]; p-value	32.16 [2.09, 494.92], 0.0128		6.59 [2.30, 18.85], 0.0004		11.77 [3.97, 34.95], <0.0001	
OR [95%-CI]; p-value	385.33 [18.25, 8136.25], <0.0001		96.00 [14.65, 629.18], <0.0001		154.00 [34.75, 682.54], <0.0001	
RD [95%-CI]; p-value	0.89 [0.77, 1.00], <0.0001		0.80 [0.63, 0.97], <0.0001		0.85 [0.75, 0.95], <0.0001	
Vist 13/ET:n/N3 (%)	32/37 (86.5)	1/17 (5.9)	32/34 (94.1)	3/21 (14.3)	64/71 (90.1)	4/38 (10.5)
RR [95%-CI]; p-value	14.70 [2.19, 98.86], 0.0057		6.59 [2.30, 18.85], 0.0004		8.56 [3.38, 21.71], <0.0001	
OR [95%-CI]; p-value	102.40 [11.02, 951.66], <0.0001		96.00 [14.65, 629.18], <0.0001		77.71 [21.24, 284.30], <0.0001	
RD [95%-CI]; p-value	0.81 [0.65, 0.96], <0.0001		0.80 [0.63, 0.97], <0.0001		0.80 [0.68, 0.92], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_1_1_m_25d30_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3935		0.4470		0.8993	
Comparison Baseline vs. EAP	0.2151		0.3589		0.1764	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	156.5 (78.86)	99.7 (11.50)	114.2 (24.99)	120.9 (32.62)	127.9 (52.27)	109.1 (24.29)
Visit 13/ET						
n/N1	13/13	5/5	27/27	3/4	40/40	8/9
Mean (SD)	129.3 (80.40)	106.4 (45.36)	86.6 (39.97)	119.3 (27.57)	100.5 (58.86)	111.3 (37.92)
EAP						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	129.1 (67.71)	96.5 (41.58)	90.1 (39.15)	104.9 (20.58)	102.8 (52.68)	100.2 (32.30)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-20.7 (17.88)	-10.2 (29.77)	-27.4 (6.62)	13.0 (19.97)	-23.0 (8.03)	2.7 (17.24)
95% CI	[-58.78, 17.45]	[-73.65, 53.25]	[-41.02, -13.86]	[-27.97, 53.97]	[-39.23, -6.84]	[-32.05, 37.49]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-10.47		-40.44		-25.75	
95% CI	[-86.56, 65.62]		[-83.65, 2.78]		[-64.72, 13.22]	
p-value	0.7733		0.0655		0.1897	
Hedges' g	-0.48		-1.20		-0.76	
95% CI	[-1.47, 0.52]		[-2.40, -0.00]		[-1.52, -0.00]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-21.6 (12.97)	-18.1 (21.60)	-24.5 (6.70)	-13.7 (17.47)	-21.7 (6.65)	-14.8 (13.06)
95% CI	[-49.27, 6.03]	[-64.16, 27.91]	[-38.19, -10.72]	[-49.49, 22.09]	[-35.12, -8.32]	[-41.16, 11.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-3.50		-10.76		-6.88	
95% CI	[-58.70, 51.71]		[-49.12, 27.61]		[-36.74, 22.98]	
p-value	0.8944		0.5704		0.6448	
Hedges' g	-0.45		-0.22		-0.39	
95% CI	[-1.44, 0.54]		[-1.25, 0.80]		[-1.11, 0.33]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	142.9 (47.70)	140.2 (41.45)	151.3 (67.41)	156.3 (59.77)	146.9 (57.89)	148.1 (51.76)
Visit 13/ET						
n/N2	101/102	56/57	90/92	55/56	191/194	111/113
Mean (SD)	111.2 (59.09)	152.5 (67.24)	118.2 (97.37)	169.0 (76.94)	114.5 (79.32)	160.7 (72.35)
EAP						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	107.0 (48.79)	150.9 (66.34)	121.0 (84.58)	162.0 (65.28)	113.6 (68.33)	156.4 (65.76)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.4 (4.81)	13.7 (6.47)	-33.7 (6.70)	12.1 (8.58)	-32.6 (4.07)	13.1 (5.33)
95% CI	[-40.91, -21.90]	[0.93, 26.47]	[-46.97, -20.47]	[-4.82, 29.09]	[-40.66, -24.64]	[2.61, 23.59]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.10		-45.85		-45.75	
95% CI	[-61.03, -29.18]		[-67.38, -24.33]		[-58.95, -32.55]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.94		-0.72		-0.81	
95% CI	[-1.28, -0.60]		[-1.06, -0.37]		[-1.06, -0.57]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-35.8 (4.06)	10.5 (5.43)	-30.5 (5.15)	5.9 (6.60)	-33.2 (3.25)	8.3 (4.26)
95% CI	[-43.80, -27.75]	[-0.28, 21.18]	[-40.62, -20.28]	[-7.11, 18.97]	[-39.56, -26.76]	[-0.05, 16.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-46.23		-36.38		-41.49	
95% CI	[-59.63, -32.82]		[-52.92, -19.84]		[-52.02, -30.95]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.12		-0.73		-0.91	
95% CI	[-1.46, -0.77]		[-1.07, -0.39]		[-1.15, -0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.1.1.1.s7.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.0863		0.1950		0.0509	
Vist 13/ET	0.3747		0.8869		0.9993	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
EAP:n/N1 (%)	2/13 (15.4)	1/5 (20.0)	10/27 (37.0)	1/4 (25.0)	12/40 (30.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.77 [0.09, 6.72], 0.8125		1.48 [0.25, 8.67], 0.6629		1.35 [0.36, 5.01], 0.6536	
OR [95%-CI]; p-value	0.73 [0.05, 10.39], 0.8139		1.76 [0.16, 19.34], 0.6387		1.50 [0.27, 8.30], 0.6407	
RD [95%-CI]; p-value	-0.05 [-0.45, 0.36], 0.8218		0.12 [-0.34, 0.58], 0.6094		0.08 [-0.23, 0.38], 0.6189	
Vist 13/ET:n/N1 (%)	5/13 (38.5)	1/5 (20.0)	14/27 (51.9)	0/4 (0.0)	19/40 (47.5)	1/9 (11.1)
RR [95%-CI]; p-value	1.92 [0.29, 12.64], 0.4961		4.67 [0.33, 65.29], 0.2525		4.28 [0.65, 27.91], 0.1291	
OR [95%-CI]; p-value	2.50 [0.21, 29.25], 0.4568		8.62 [0.41, 179.27], 0.1084		7.24 [0.83, 63.36], 0.0448	
RD [95%-CI]; p-value	0.18 [-0.25, 0.62], 0.4100		0.41 [0.06, 0.75], 0.0211		0.36 [0.11, 0.62], 0.0055	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
EAP:n/N2 (%)	44/102 (43.1)	4/57 (7.0)	37/92 (40.2)	4/56 (7.1)	81/194 (41.8)	8/113 (7.1)
RR [95%-CI]; p-value	6.15 [2.33, 16.23], 0.0002		5.63 [2.12, 14.95], 0.0005		5.90 [2.96, 11.74], <0.0001	
OR [95%-CI]; p-value	10.05 [3.38, 29.87], <0.0001		8.75 [2.91, 26.25], <0.0001		9.41 [4.34, 20.39], <0.0001	
RD [95%-CI]; p-value	0.36 [0.24, 0.48], <0.0001		0.33 [0.21, 0.45], <0.0001		0.35 [0.26, 0.43], <0.0001	
Vist 13/ET:n/N2 (%)	44/102 (43.1)	5/57 (8.8)	44/92 (47.8)	7/56 (12.5)	88/194 (45.4)	12/113 (10.6)
RR [95%-CI]; p-value	4.92 [2.07, 11.70], 0.0003		3.83 [1.85, 7.90], 0.0003		4.27 [2.45, 7.45], <0.0001	
OR [95%-CI]; p-value	7.89 [2.91, 21.40], <0.0001		6.42 [2.63, 15.65], <0.0001		6.99 [3.60, 13.54], <0.0001	
RD [95%-CI]; p-value	0.34 [0.22, 0.46], <0.0001		0.35 [0.22, 0.49], <0.0001		0.35 [0.26, 0.44], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_1_1_1_m_pth30pct_dose_pp.sas using SAS 9.4

Table 12.2.1.1.2.s7.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3697		0.3050		0.1885	
Vist 13/ET	0.8217		0.8143		0.8625	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
EAP:n/N1 (%)	9/13 (69.2)	2/5 (40.0)	20/27 (74.1)	2/4 (50.0)	29/40 (72.5)	4/9 (44.4)
RR [95%-CI]; p-value	1.73 [0.56, 5.37], 0.3427		1.48 [0.54, 4.05], 0.4434		1.63 [0.77, 3.47], 0.2039	
OR [95%-CI]; p-value	3.38 [0.40, 28.74], 0.2545		2.86 [0.34, 24.30], 0.3222		3.30 [0.75, 14.57], 0.1049	
RD [95%-CI]; p-value	0.29 [-0.21, 0.79], 0.2493		0.24 [-0.28, 0.76], 0.3615		0.28 [-0.07, 0.63], 0.1192	
Vist 13/ET:n/N1 (%)	6/13 (46.2)	1/5 (20.0)	20/27 (74.1)	1/4 (25.0)	26/40 (65.0)	2/9 (22.2)
RR [95%-CI]; p-value	2.31 [0.36, 14.66], 0.3753		2.96 [0.53, 16.41], 0.2137		2.93 [0.84, 10.14], 0.0906	
OR [95%-CI]; p-value	3.43 [0.30, 39.64], 0.3080		8.57 [0.76, 96.52], 0.0501		6.50 [1.19, 35.60], 0.0191	
RD [95%-CI]; p-value	0.26 [-0.18, 0.70], 0.2474		0.49 [0.04, 0.95], 0.0347		0.43 [0.12, 0.74], 0.0067	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
EAP:n/N2 (%)	76/102 (74.5)	14/57 (24.6)	65/92 (70.7)	15/56 (26.8)	141/194 (72.7)	29/113 (25.7)
RR [95%-CI]; p-value	3.03 [1.90, 4.85], <0.0001		2.64 [1.68, 4.15], <0.0001		2.83 [2.05, 3.92], <0.0001	
OR [95%-CI]; p-value	8.98 [4.24, 19.00], <0.0001		6.58 [3.13, 13.82], <0.0001		7.71 [4.55, 13.05], <0.0001	
RD [95%-CI]; p-value	0.50 [0.36, 0.64], <0.0001		0.44 [0.29, 0.59], <0.0001		0.47 [0.37, 0.57], <0.0001	
Vist 13/ET:n/N2 (%)	72/102 (70.6)	14/57 (24.6)	67/92 (72.8)	17/56 (30.4)	139/194 (71.6)	31/113 (27.4)
RR [95%-CI]; p-value	2.87 [1.79, 4.61], <0.0001		2.40 [1.58, 3.64], <0.0001		2.61 [1.91, 3.57], <0.0001	
OR [95%-CI]; p-value	7.37 [3.52, 15.42], <0.0001		6.15 [2.96, 12.78], <0.0001		6.69 [3.98, 11.22], <0.0001	
RD [95%-CI]; p-value	0.46 [0.32, 0.60], <0.0001		0.42 [0.27, 0.58], <0.0001		0.44 [0.34, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_1_1_2_m_pth10pct_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3195		0.6183		0.8555	
Comparison Baseline vs. EAP	0.2169		0.8128		0.3754	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	19.3 (5.12)	17.5 (6.97)	22.0 (5.80)	19.2 (6.21)	21.1 (5.66)	18.2 (6.29)
Visit 13/ET						
n/N1	13/13	5/5	27/27	3/4	40/40	8/9
Mean (SD)	52.7 (19.53)	18.8 (7.98)	65.0 (16.48)	18.0 (5.29)	61.0 (18.23)	18.5 (6.68)
EAP						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	52.4 (19.21)	20.0 (8.03)	64.6 (17.97)	16.9 (5.33)	60.6 (19.05)	18.6 (6.74)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	32.9 (3.95)	2.5 (6.40)	43.0 (2.96)	-4.2 (8.89)	38.2 (2.54)	-1.2 (5.50)
95% CI	[24.52, 41.34]	[-11.11, 16.15]	[36.91, 49.06]	[-22.43, 14.03]	[33.11, 43.35]	[-12.29, 9.91]
Diff in LS-Mean [ER-Calcifediol - Placebo]	30.41		47.19		39.42	
95% CI	[14.32, 46.50]		[27.97, 66.41]		[27.20, 51.63]	
p-value	0.0011		<0.0001		<0.0001	
Hedges' g	2.09		3.04		2.62	
95% CI	[0.89, 3.28]		[1.65, 4.43]		[1.71, 3.53]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	32.6 (3.86)	3.7 (6.25)	42.7 (3.15)	-2.2 (8.27)	37.8 (2.62)	0.8 (5.29)
95% CI	[24.37, 40.82]	[-9.67, 16.99]	[36.21, 49.12]	[-19.17, 14.73]	[32.55, 43.12]	[-9.85, 11.48]
Diff in LS-Mean [ER-Calcifediol - Placebo]	28.94		44.88		37.02	
95% CI	[13.20, 44.67]		[26.69, 63.08]		[25.11, 48.94]	
p-value	0.0014		<0.0001		<0.0001	
Hedges' g	2.03		2.72		2.45	
95% CI	[0.85, 3.22]		[1.49, 3.95]		[1.59, 3.31]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	19.9 (5.15)	19.4 (5.59)	18.9 (5.31)	19.3 (5.65)	19.4 (5.24)	19.3 (5.60)
Visit 13/ET						
n/N2	102/102	56/57	90/92	54/56	192/194	110/113
Mean (SD)	69.7 (23.75)	17.3 (6.22)	70.5 (24.06)	20.1 (7.03)	70.1 (23.84)	18.7 (6.75)
EAP						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	68.7 (22.28)	17.5 (6.14)	68.1 (21.71)	19.7 (6.62)	68.4 (21.96)	18.6 (6.45)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.8 (1.88)	-2.2 (2.53)	51.5 (2.01)	0.7 (2.60)	50.7 (1.37)	-0.8 (1.81)
95% CI	[46.09, 53.51]	[-7.21, 2.80]	[47.56, 55.51]	[-4.46, 5.81]	[47.97, 53.37]	[-4.34, 2.78]
Diff in LS-Mean [ER-Calcifediol - Placebo]	52.01		50.87		51.45	
95% CI	[45.78, 58.24]		[44.37, 57.36]		[46.98, 55.92]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.74		2.67		2.71	
95% CI	[2.29, 3.18]		[2.21, 3.12]		[2.39, 3.03]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	48.8 (1.77)	-2.0 (2.36)	49.1 (1.76)	0.4 (2.26)	48.9 (1.25)	-0.7 (1.63)
95% CI	[45.30, 52.27]	[-6.63, 2.70]	[45.64, 52.61]	[-4.04, 4.88]	[46.49, 51.40]	[-3.96, 2.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.75		48.70		49.69	
95% CI	[44.92, 56.58]		[43.04, 54.36]		[45.65, 53.73]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.83		2.88		2.86	
95% CI	[2.38, 3.28]		[2.41, 3.35]		[2.54, 3.19]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.1.1.s7.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.0644		0.8842		0.4775	
Vist 13/ET	0.4999		0.9941		0.8245	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
EAP:n/N1 (%)	12/13 (92.3)	1/5 (20.0)	27/27 (100.0)	0/4 (0.0)	39/40 (97.5)	1/9 (11.1)
RR [95%-CI]; p-value	4.62 [0.79, 26.83], 0.0885		8.84 [0.65, 120.62], 0.1023		8.78 [1.38, 55.73], 0.0213	
OR [95%-CI]; p-value	48.00 [2.40, 958.24], 0.0022		432.00 [7.47, 24998.29], <0.0001		312.00 [17.61, 5526.46], <0.0001	
RD [95%-CI]; p-value	0.72 [0.34, 1.00], 0.0002		0.87 [0.58, 1.00], <0.0001		0.86 [0.65, 1.00], <0.0001	
Vist 13/ET:n/N1 (%)	11/13 (84.6)	0/5 (0.0)	27/27 (100.0)	0/4 (0.0)	38/40 (95.0)	0/9 (0.0)
RR [95%-CI]; p-value	9.31 [0.66, 132.13], 0.0993		8.84 [0.65, 120.62], 0.1023		18.05 [1.21, 268.26], 0.0356	
OR [95%-CI]; p-value	55.00 [2.08, 1453.39], 0.0022		432.00 [7.47, 24998.29], <0.0001		342.00 [14.18, 8248.80], <0.0001	
RD [95%-CI]; p-value	0.76 [0.45, 1.00], <0.0001		0.87 [0.58, 1.00], <0.0001		0.90 [0.74, 1.00], <0.0001	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
EAP:n/N2 (%)	98/102 (96.1)	1/57 (1.8)	89/92 (96.7)	5/56 (8.9)	187/194 (96.4)	6/113 (5.3)
RR [95%-CI]; p-value	54.76 [7.85, 382.27], <0.0001		10.83 [4.69, 25.03], <0.0001		18.15 [8.33, 39.57], <0.0001	
OR [95%-CI]; p-value	1372.00 [149.64, 12579.09], <0.0001		302.60 [69.43, 1318.93], <0.0001		476.40 [156.06, 1454.29], <0.0001	
RD [95%-CI]; p-value	0.94 [0.89, 0.99], <0.0001		0.88 [0.80, 0.96], <0.0001		0.91 [0.86, 0.96], <0.0001	
Vist 13/ET:n/N2 (%)	93/102 (91.2)	2/57 (3.5)	88/92 (95.7)	6/56 (10.7)	181/194 (93.3)	8/113 (7.1)
RR [95%-CI]; p-value	25.99 [6.65, 101.52], <0.0001		8.93 [4.19, 19.04], <0.0001		13.18 [6.75, 25.73], <0.0001	
OR [95%-CI]; p-value	284.17 [59.24, 1363.20], <0.0001		183.33 [49.37, 680.76], <0.0001		182.74 [73.34, 455.33], <0.0001	
RD [95%-CI]; p-value	0.88 [0.80, 0.95], <0.0001		0.85 [0.76, 0.94], <0.0001		0.86 [0.80, 0.92], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_1_1_m_25d30_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6567		0.5498		0.3113	
Comparison Baseline vs. EAP	0.4305		0.3930		0.1301	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	164.9 (57.31)	123.8 (31.83)	147.6 (64.09)	145.2 (30.11)	155.2 (60.91)	133.3 (32.08)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	116.7 (48.97)	117.6 (40.67)	128.0 (141.99)	179.1 (81.88)	123.0 (109.76)	144.9 (68.01)
EAP						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	114.3 (53.87)	115.5 (43.58)	134.9 (131.63)	171.3 (59.47)	125.8 (103.87)	140.3 (57.24)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-36.6 (11.92)	-23.6 (14.85)	-20.1 (19.00)	35.1 (29.28)	-35.2 (13.39)	15.9 (18.42)
95% CI	[-61.32, -11.87]	[-54.44, 7.16]	[-59.31, 19.11]	[-25.30, 95.57]	[-62.16, -8.30]	[-21.18, 52.94]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-12.95		-55.23		-51.11	
95% CI	[-54.01, 28.11]		[-127.28, 16.81]		[-97.36, -4.87]	
p-value	0.5198		0.1267		0.0310	
Hedges' g	-0.73		-0.57		-0.56	
95% CI	[-1.53, 0.07]		[-1.38, 0.25]		[-1.14, 0.01]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-41.5 (12.34)	-22.1 (15.37)	-13.1 (17.20)	27.0 (26.51)	-32.7 (12.04)	10.4 (16.57)
95% CI	[-67.12, -15.92]	[-53.96, 9.81]	[-48.61, 22.39]	[-27.69, 81.73]	[-56.93, -8.50]	[-22.90, 43.75]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-19.45		-40.13		-43.15	
95% CI	[-61.95, 23.06]		[-105.36, 25.09]		[-84.73, -1.56]	
p-value	0.3530		0.2163		0.0423	
Hedges' g	-0.78		-0.47		-0.51	
95% CI	[-1.58, 0.03]		[-1.28, 0.34]		[-1.08, 0.06]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	141.4 (50.58)	139.4 (42.73)	142.0 (62.29)	155.2 (62.20)	141.7 (56.60)	147.3 (53.69)
Visit 13/ET						
n/N2	99/100	51/52	98/100	50/52	197/200	101/104
Mean (SD)	112.7 (63.63)	154.8 (69.31)	107.6 (74.38)	164.4 (75.56)	110.2 (69.05)	159.5 (72.27)
EAP						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	108.7 (51.25)	152.5 (68.37)	110.0 (62.69)	156.2 (65.90)	109.4 (57.12)	154.3 (66.84)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-28.4 (4.94)	17.1 (6.89)	-35.3 (5.18)	9.9 (7.26)	-31.8 (3.57)	13.4 (4.99)
95% CI	[-38.17, -18.64]	[3.51, 30.73]	[-45.58, -25.11]	[-4.45, 24.25]	[-38.84, -24.79]	[3.58, 23.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.52		-45.24		-45.21	
95% CI	[-62.28, -28.77]		[-62.91, -27.57]		[-57.29, -33.14]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.93		-0.84		-0.88	
95% CI	[-1.28, -0.58]		[-1.19, -0.49]		[-1.13, -0.64]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.5 (3.99)	12.9 (5.53)	-32.8 (3.73)	2.4 (5.18)	-32.6 (2.73)	7.6 (3.78)
95% CI	[-40.41, -24.65]	[1.98, 23.85]	[-40.12, -25.39]	[-7.86, 12.61]	[-37.97, -27.24]	[0.13, 15.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.45		-35.13		-40.18	
95% CI	[-58.92, -31.97]		[-47.77, -22.49]		[-49.36, -31.00]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.13		-0.85		-0.99	
95% CI	[-1.49, -0.77]		[-1.20, -0.50]		[-1.24, -0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.1.1.1.s8.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.1722		0.6985		0.6761	
Vist 13/ET	0.9513		0.5815		0.4571	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
EAP:n/N1 (%)	6/15 (40.0)	2/10 (20.0)	8/19 (42.1)	0/8 (0.0)	14/34 (41.2)	2/18 (11.1)
RR [95%-CI]; p-value	2.00 [0.50, 8.00], 0.3270		7.16 [0.46, 110.88], 0.1592		3.71 [0.94, 14.54], 0.0604	
OR [95%-CI]; p-value	2.67 [0.41, 17.17], 0.2936		11.64 [0.58, 233.43], 0.0575		5.60 [1.11, 28.32], 0.0254	
RD [95%-CI]; p-value	0.20 [-0.15, 0.55], 0.2636		0.36 [0.09, 0.63], 0.0092		0.30 [0.08, 0.52], 0.0074	
Vist 13/ET:n/N1 (%)	7/15 (46.7)	1/10 (10.0)	9/19 (47.4)	0/8 (0.0)	16/34 (47.1)	1/18 (5.6)
RR [95%-CI]; p-value	4.67 [0.67, 32.36], 0.1190		8.05 [0.52, 123.53], 0.1343		8.47 [1.22, 58.82], 0.0307	
OR [95%-CI]; p-value	7.88 [0.79, 78.67], 0.0542		14.40 [0.72, 287.98], 0.0345		15.11 [1.80, 126.68], 0.0024	
RD [95%-CI]; p-value	0.37 [0.05, 0.68], 0.0219		0.41 [0.14, 0.69], 0.0031		0.42 [0.22, 0.61], <0.0001	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
EAP:n/N2 (%)	40/100 (40.0)	3/52 (5.8)	39/100 (39.0)	5/52 (9.6)	79/200 (39.5)	8/104 (7.7)
RR [95%-CI]; p-value	6.93 [2.25, 21.34], 0.0007		4.06 [1.70, 9.67], 0.0016		5.14 [2.58, 10.21], <0.0001	
OR [95%-CI]; p-value	10.89 [3.17, 37.34], <0.0001		6.01 [2.20, 16.43], 0.0002		7.83 [3.61, 17.01], <0.0001	
RD [95%-CI]; p-value	0.34 [0.23, 0.46], <0.0001		0.29 [0.17, 0.42], <0.0001		0.32 [0.23, 0.40], <0.0001	
Vist 13/ET:n/N2 (%)	42/100 (42.0)	5/52 (9.6)	49/100 (49.0)	7/52 (13.5)	91/200 (45.5)	12/104 (11.5)
RR [95%-CI]; p-value	4.37 [1.84, 10.37], 0.0008		3.64 [1.78, 7.46], 0.0004		3.94 [2.27, 6.86], <0.0001	
OR [95%-CI]; p-value	6.81 [2.49, 18.57], <0.0001		6.18 [2.54, 15.00], <0.0001		6.40 [3.30, 12.42], <0.0001	
RD [95%-CI]; p-value	0.32 [0.20, 0.45], <0.0001		0.36 [0.22, 0.49], <0.0001		0.34 [0.25, 0.43], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_1_1_1_m_pth30pct_vitd_pp.sas using SAS 9.4

Table 12.2.1.1.2.s8.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.7347		0.8909		0.8800	
Vist 13/ET	0.1354		0.6499		0.5247	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
EAP:n/N1 (%)	11/15 (73.3)	3/10 (30.0)	13/19 (68.4)	2/8 (25.0)	24/34 (70.6)	5/18 (27.8)
RR [95%-CI]; p-value	2.44 [0.90, 6.61], 0.0782		2.74 [0.79, 9.44], 0.1111		2.54 [1.17, 5.52], 0.0185	
OR [95%-CI]; p-value	6.42 [1.09, 37.73], 0.0325		6.50 [1.00, 42.17], 0.0381		6.24 [1.76, 22.18], 0.0031	
RD [95%-CI]; p-value	0.43 [0.07, 0.79], 0.0188		0.43 [0.07, 0.80], 0.0199		0.43 [0.17, 0.69], 0.0011	
Vist 13/ET:n/N1 (%)	9/15 (60.0)	4/10 (40.0)	15/19 (78.9)	2/8 (25.0)	24/34 (70.6)	6/18 (33.3)
RR [95%-CI]; p-value	1.50 [0.63, 3.56], 0.3578		3.16 [0.93, 10.72], 0.0652		2.12 [1.06, 4.22], 0.0327	
OR [95%-CI]; p-value	2.25 [0.44, 11.52], 0.3268		11.25 [1.61, 78.57], 0.0080		4.80 [1.41, 16.37], 0.0097	
RD [95%-CI]; p-value	0.20 [-0.19, 0.59], 0.3173		0.54 [0.19, 0.89], 0.0026		0.37 [0.11, 0.64], 0.0061	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
EAP:n/N2 (%)	74/100 (74.0)	13/52 (25.0)	72/100 (72.0)	15/52 (28.8)	146/200 (73.0)	28/104 (26.9)
RR [95%-CI]; p-value	2.96 [1.82, 4.81], <0.0001		2.50 [1.60, 3.89], <0.0001		2.71 [1.95, 3.76], <0.0001	
OR [95%-CI]; p-value	8.54 [3.95, 18.45], <0.0001		6.34 [3.02, 13.32], <0.0001		7.34 [4.30, 12.52], <0.0001	
RD [95%-CI]; p-value	0.49 [0.34, 0.64], <0.0001		0.43 [0.28, 0.58], <0.0001		0.46 [0.36, 0.57], <0.0001	
Vist 13/ET:n/N2 (%)	69/100 (69.0)	11/52 (21.2)	72/100 (72.0)	16/52 (30.8)	141/200 (70.5)	27/104 (26.0)
RR [95%-CI]; p-value	3.26 [1.90, 5.60], <0.0001		2.34 [1.53, 3.58], <0.0001		2.72 [1.94, 3.80], <0.0001	
OR [95%-CI]; p-value	8.30 [3.77, 18.26], <0.0001		5.79 [2.78, 12.04], <0.0001		6.82 [4.00, 11.62], <0.0001	
RD [95%-CI]; p-value	0.48 [0.34, 0.62], <0.0001		0.41 [0.26, 0.57], <0.0001		0.45 [0.34, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_1_1_2_m_pth10pct_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6607		0.9228		0.8641	
Comparison Baseline vs. EAP	0.2840		0.7377		0.2947	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	22.2 (5.36)	18.6 (4.81)	20.8 (5.16)	23.7 (4.46)	21.4 (5.22)	20.9 (5.21)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	66.1 (20.15)	21.1 (7.69)	69.6 (20.80)	27.5 (4.11)	68.0 (20.29)	23.9 (7.00)
EAP						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	63.2 (12.95)	21.7 (7.37)	66.6 (18.13)	26.4 (3.47)	65.1 (15.91)	23.8 (6.27)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.8 (4.42)	1.1 (5.49)	48.9 (4.02)	3.7 (6.29)	46.4 (2.93)	3.1 (4.02)
95% CI	[35.58, 53.93]	[-10.28, 12.48]	[40.55, 57.16]	[-9.27, 16.70]	[40.50, 52.29]	[-4.95, 11.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	43.65		45.14		43.26	
95% CI	[28.61, 58.69]		[29.49, 60.78]		[33.24, 53.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.40		2.57		2.58	
95% CI	[1.38, 3.42]		[1.51, 3.62]		[1.83, 3.33]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	41.5 (2.88)	2.3 (3.57)	46.1 (3.28)	1.9 (5.13)	43.4 (2.20)	2.9 (3.01)
95% CI	[35.57, 47.51]	[-5.10, 9.71]	[39.34, 52.89]	[-8.69, 12.50]	[38.96, 47.80]	[-3.14, 8.98]
Diff in LS-Mean [ER-Calcifediol - Placebo]	39.23		44.21		40.46	
95% CI	[29.45, 49.02]		[31.44, 56.97]		[32.96, 47.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.39		2.98		3.22	
95% CI	[2.17, 4.60]		[1.85, 4.11]		[2.38, 4.05]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	19.5 (5.02)	19.4 (5.86)	19.4 (5.62)	18.6 (5.52)	19.4 (5.32)	19.0 (5.68)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	68.0 (24.44)	16.7 (5.83)	69.2 (23.03)	18.8 (6.52)	68.6 (23.70)	17.7 (6.23)
EAP						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	67.4 (23.58)	16.9 (5.80)	67.4 (21.47)	18.4 (6.27)	67.4 (22.49)	17.7 (6.06)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.5 (1.93)	-2.7 (2.71)	49.8 (1.91)	-0.3 (2.70)	49.2 (1.36)	-1.5 (1.91)
95% CI	[44.72, 52.36]	[-8.09, 2.61]	[46.02, 53.57]	[-5.65, 5.03]	[46.48, 51.83]	[-5.26, 2.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.28		50.10		50.65	
95% CI	[44.71, 57.85]		[43.56, 56.65]		[46.02, 55.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.65		2.62		2.65	
95% CI	[2.20, 3.10]		[2.17, 3.08]		[2.33, 2.97]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.9 (1.88)	-2.4 (2.60)	48.1 (1.73)	-0.2 (2.40)	48.0 (1.27)	-1.3 (1.77)
95% CI	[44.16, 51.58]	[-7.57, 2.70]	[44.65, 51.49]	[-4.99, 4.50]	[45.45, 50.47]	[-4.80, 2.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.30		48.32		49.28	
95% CI	[43.97, 56.64]		[42.46, 54.17]		[44.99, 53.57]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.68		2.78		2.74	
95% CI	[2.23, 3.13]		[2.32, 3.23]		[2.42, 3.06]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.1.1.s8.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.0500		0.0714		0.0047	
Vist 13/ET	0.0515		0.0089		0.0010	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
EAP:n/N1 (%)	15/15 (100.0)	2/10 (20.0)	18/19 (94.7)	2/8 (25.0)	33/34 (97.1)	4/18 (22.2)
RR [95%-CI]; p-value	4.84 [1.40, 16.77], 0.0129		3.79 [1.14, 12.64], 0.0302		4.37 [1.84, 10.39], 0.0009	
OR [95%-CI]; p-value	120.00 [4.82, 2990.12], <0.0001		54.00 [4.12, 707.06], 0.0002		115.50 [11.83, 1127.78], <0.0001	
RD [95%-CI]; p-value	0.77 [0.50, 1.00], <0.0001		0.70 [0.38, 1.00], <0.0001		0.75 [0.55, 0.95], <0.0001	
Vist 13/ET:n/N1 (%)	14/15 (93.3)	2/10 (20.0)	18/19 (94.7)	3/8 (37.5)	32/34 (94.1)	5/18 (27.8)
RR [95%-CI]; p-value	4.67 [1.34, 16.24], 0.0155		2.53 [1.03, 6.22], 0.0438		3.39 [1.60, 7.17], 0.0014	
OR [95%-CI]; p-value	56.00 [4.36, 719.20], 0.0002		30.00 [2.54, 354.87], 0.0011		41.60 [7.14, 242.28], <0.0001	
RD [95%-CI]; p-value	0.73 [0.46, 1.00], <0.0001		0.57 [0.22, 0.92], 0.0014		0.66 [0.44, 0.88], <0.0001	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
EAP:n/N2 (%)	95/100 (95.0)	0/52 (0.0)	98/100 (98.0)	3/52 (5.8)	193/200 (96.5)	3/104 (2.9)
RR [95%-CI]; p-value	99.75 [6.32, 1574.37], 0.0011		16.99 [5.66, 50.97], <0.0001		33.45 [10.96, 102.06], <0.0001	
OR [95%-CI]; p-value	1976.00 [105.86, 36883.55], <0.0001		800.33 [129.45, 4948.25], <0.0001		928.24 [234.99, 3666.69], <0.0001	
RD [95%-CI]; p-value	0.94 [0.89, 0.99], <0.0001		0.92 [0.85, 0.99], <0.0001		0.94 [0.90, 0.98], <0.0001	
Vist 13/ET:n/N2 (%)	90/100 (90.0)	0/52 (0.0)	97/100 (97.0)	3/52 (5.8)	187/200 (93.5)	3/104 (2.9)
RR [95%-CI]; p-value	94.50 [5.98, 1492.12], 0.0012		16.81 [5.60, 50.46], <0.0001		32.41 [10.62, 98.92], <0.0001	
OR [95%-CI]; p-value	936.00 [53.57, 16355.48], <0.0001		528.11 [102.78, 2713.69], <0.0001		484.28 [134.85, 1739.18], <0.0001	
RD [95%-CI]; p-value	0.89 [0.83, 0.95], <0.0001		0.91 [0.84, 0.98], <0.0001		0.91 [0.86, 0.95], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_1_1_m_25d30_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3926		0.0994		0.4801	
Comparison Baseline vs. EAP	0.2420		0.0833		0.5648	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	145.7 (46.95)	137.2 (44.69)	160.3 (78.17)	160.8 (57.61)	153.0 (64.75)	148.1 (52.01)
Visit 13/ET						
n/N1	57/58	34/35	58/59	28/30	115/117	62/65
Mean (SD)	114.7 (65.26)	153.2 (71.44)	127.7 (116.10)	168.6 (69.67)	121.3 (94.21)	160.2 (70.49)
EAP						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	108.6 (51.37)	151.2 (71.50)	130.2 (100.53)	159.4 (62.15)	119.5 (80.42)	155.0 (66.95)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.0 (6.58)	19.2 (8.53)	-33.5 (9.56)	6.8 (13.76)	-32.2 (5.76)	13.0 (7.88)
95% CI	[-44.03, -17.89]	[2.21, 36.12]	[-52.53, -14.50]	[-20.56, 34.18]	[-43.60, -20.86]	[-2.59, 28.52]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-50.12		-40.32		-45.20	
95% CI	[-71.60, -28.65]		[-73.65, -7.00]		[-64.47, -25.92]	
p-value	<0.0001		0.0183		<0.0001	
Hedges' g	-1.00		-0.55		-0.74	
95% CI	[-1.45, -0.56]		[-1.01, -0.10]		[-1.06, -0.42]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.8 (5.47)	13.7 (7.04)	-30.1 (7.47)	-1.4 (10.47)	-33.5 (4.60)	6.2 (6.19)
95% CI	[-47.69, -25.97]	[-0.29, 27.69]	[-44.92, -15.22]	[-22.21, 19.43]	[-42.55, -24.38]	[-6.01, 18.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-50.53		-28.68		-39.68	
95% CI	[-68.27, -32.78]		[-54.25, -3.10]		[-54.92, -24.45]	
p-value	<0.0001		0.0284		<0.0001	
Hedges' g	-1.22		-0.50		-0.81	
95% CI	[-1.67, -0.77]		[-0.94, -0.06]		[-1.12, -0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	143.2 (56.81)	136.6 (37.40)	125.8 (34.18)	147.1 (60.26)	134.3 (47.20)	142.1 (50.57)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	111.8 (58.52)	143.0 (60.98)	94.3 (42.60)	164.3 (82.39)	102.9 (51.57)	154.2 (73.19)
EAP						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	110.3 (51.86)	140.4 (59.29)	98.0 (39.89)	157.0 (68.41)	104.0 (46.32)	149.2 (64.23)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.6 (6.50)	4.9 (9.45)	-31.9 (5.73)	18.8 (8.10)	-31.8 (4.32)	13.1 (6.18)
95% CI	[-43.55, -17.68]	[-13.86, 23.74]	[-43.24, -20.47]	[2.67, 34.87]	[-40.34, -23.26]	[0.86, 25.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.56		-50.62		-44.86	
95% CI	[-58.40, -12.72]		[-70.57, -30.67]		[-59.78, -29.95]	
p-value	0.0027		<0.0001		<0.0001	
Hedges' g	-0.72		-1.10		-0.91	
95% CI	[-1.19, -0.26]		[-1.56, -0.63]		[-1.24, -0.58]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.2 (5.44)	2.5 (7.91)	-28.9 (4.53)	12.1 (6.46)	-30.9 (3.52)	8.1 (5.05)
95% CI	[-43.05, -21.38]	[-13.23, 18.27]	[-37.89, -19.90]	[-0.69, 24.98]	[-37.82, -23.94]	[-1.87, 18.06]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-34.74		-41.04		-38.98	
95% CI	[-53.86, -15.61]		[-56.89, -25.19]		[-51.14, -26.82]	
p-value	0.0005		<0.0001		<0.0001	
Hedges' g	-0.83		-1.06		-0.94	
95% CI	[-1.30, -0.36]		[-1.52, -0.60]		[-1.27, -0.61]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.1.1.1.s9.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4173		0.1002		0.2816	
Vist 13/ET	0.2537		0.2363		0.9393	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
EAP:n/N1 (%)	24/58 (41.4)	2/35 (5.7)	22/59 (37.3)	5/30 (16.7)	46/117 (39.3)	7/65 (10.8)
RR [95%-CI]; p-value	7.24 [1.82, 28.79], 0.0049		2.24 [0.94, 5.32], 0.0683		3.65 [1.75, 7.61], 0.0006	
OR [95%-CI]; p-value	11.65 [2.55, 53.25], 0.0002		2.97 [0.99, 8.89], 0.0455		5.37 [2.25, 12.78], <0.0001	
RD [95%-CI]; p-value	0.36 [0.21, 0.50], <0.0001		0.21 [0.02, 0.39], 0.0261		0.29 [0.17, 0.40], <0.0001	
Vist 13/ET:n/N1 (%)	25/58 (43.1)	2/35 (5.7)	28/59 (47.5)	5/30 (16.7)	53/117 (45.3)	7/65 (10.8)
RR [95%-CI]; p-value	7.54 [1.90, 29.92], 0.0040		2.85 [1.22, 6.62], 0.0151		4.21 [2.03, 8.71], 0.0001	
OR [95%-CI]; p-value	12.50 [2.74, 57.09], 0.0001		4.52 [1.52, 13.40], 0.0045		6.86 [2.89, 16.29], <0.0001	
RD [95%-CI]; p-value	0.37 [0.23, 0.52], <0.0001		0.31 [0.12, 0.49], 0.0011		0.35 [0.23, 0.46], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
EAP:n/N2 (%)	22/57 (38.6)	3/27 (11.1)	25/60 (41.7)	0/30 (0.0)	47/117 (40.2)	3/57 (5.3)
RR [95%-CI]; p-value	3.47 [1.14, 10.60], 0.0287		25.42 [1.60, 403.69], 0.0218		7.63 [2.48, 23.47], 0.0004	
OR [95%-CI]; p-value	5.03 [1.35, 18.70], 0.0101		42.86 [2.50, 734.67], <0.0001		12.09 [3.57, 40.93], <0.0001	
RD [95%-CI]; p-value	0.27 [0.10, 0.45], 0.0019		0.40 [0.27, 0.53], <0.0001		0.35 [0.24, 0.46], <0.0001	
Vist 13/ET:n/N2 (%)	24/57 (42.1)	4/27 (14.8)	30/60 (50.0)	2/30 (6.7)	54/117 (46.2)	6/57 (10.5)
RR [95%-CI]; p-value	2.84 [1.09, 7.38], 0.0319		7.50 [1.92, 29.30], 0.0038		4.38 [2.01, 9.58], 0.0002	
OR [95%-CI]; p-value	4.18 [1.28, 13.68], 0.0132		14.00 [3.06, 64.09], <0.0001		7.29 [2.90, 18.29], <0.0001	
RD [95%-CI]; p-value	0.27 [0.09, 0.46], 0.0039		0.43 [0.28, 0.59], <0.0001		0.36 [0.24, 0.48], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_1_1_1_m_pth30pct_bl25d_pp.sas using SAS 9.4

Table 12.2.1.1.2.s9.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.5492		0.6102		0.9494	
Vist 13/ET	0.2124		0.8987		0.4152	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
EAP:n/N1 (%)	43/58 (74.1)	8/35 (22.9)	45/59 (76.3)	10/30 (33.3)	88/117 (75.2)	18/65 (27.7)
RR [95%-CI]; p-value	3.24 [1.73, 6.07], 0.0002		2.29 [1.35, 3.87], 0.0020		2.72 [1.81, 4.08], <0.0001	
OR [95%-CI]; p-value	9.68 [3.62, 25.88], <0.0001		6.43 [2.44, 16.92], <0.0001		7.92 [3.99, 15.74], <0.0001	
RD [95%-CI]; p-value	0.51 [0.33, 0.69], <0.0001		0.43 [0.23, 0.63], <0.0001		0.48 [0.34, 0.61], <0.0001	
Vist 13/ET:n/N1 (%)	38/58 (65.5)	6/35 (17.1)	42/59 (71.2)	9/30 (30.0)	80/117 (68.4)	15/65 (23.1)
RR [95%-CI]; p-value	3.82 [1.80, 8.11], 0.0005		2.37 [1.34, 4.20], 0.0030		2.96 [1.87, 4.70], <0.0001	
OR [95%-CI]; p-value	9.18 [3.27, 25.79], <0.0001		5.76 [2.20, 15.10], 0.0002		7.21 [3.59, 14.46], <0.0001	
RD [95%-CI]; p-value	0.48 [0.31, 0.66], <0.0001		0.41 [0.21, 0.61], <0.0001		0.45 [0.32, 0.59], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
EAP:n/N2 (%)	42/57 (73.7)	8/27 (29.6)	40/60 (66.7)	7/30 (23.3)	82/117 (70.1)	15/57 (26.3)
RR [95%-CI]; p-value	2.49 [1.36, 4.54], 0.0030		2.86 [1.46, 5.60], 0.0022		2.66 [1.70, 4.18], <0.0001	
OR [95%-CI]; p-value	6.65 [2.41, 18.35], 0.0001		6.57 [2.41, 17.90], 0.0001		6.56 [3.23, 13.34], <0.0001	
RD [95%-CI]; p-value	0.44 [0.23, 0.65], <0.0001		0.43 [0.24, 0.63], <0.0001		0.44 [0.30, 0.58], <0.0001	
Vist 13/ET:n/N2 (%)	40/57 (70.2)	9/27 (33.3)	45/60 (75.0)	9/30 (30.0)	85/117 (72.6)	18/57 (31.6)
RR [95%-CI]; p-value	2.11 [1.20, 3.68], 0.0091		2.50 [1.42, 4.40], 0.0015		2.30 [1.55, 3.43], <0.0001	
OR [95%-CI]; p-value	4.71 [1.76, 12.55], 0.0014		7.00 [2.64, 18.56], <0.0001		5.76 [2.88, 11.48], <0.0001	
RD [95%-CI]; p-value	0.37 [0.15, 0.58], 0.0007		0.45 [0.25, 0.65], <0.0001		0.41 [0.27, 0.56], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_1_1_2_m_pth10pct_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1498		0.0257		0.0103	
Comparison Baseline vs. EAP	0.0924		0.3727		0.0645	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	15.4 (2.58)	15.1 (3.09)	15.0 (3.27)	14.8 (3.25)	15.2 (2.95)	14.9 (3.14)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	61.9 (25.22)	14.2 (4.89)	65.4 (25.88)	16.4 (6.22)	63.7 (25.50)	15.2 (5.58)
EAP						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	62.3 (25.00)	14.4 (4.95)	62.3 (21.36)	15.9 (5.42)	62.3 (23.14)	15.1 (5.18)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.5 (2.66)	-0.8 (3.47)	50.4 (2.86)	1.4 (4.19)	48.5 (1.94)	0.2 (2.70)
95% CI	[41.20, 51.76]	[-7.75, 6.05]	[44.71, 56.08]	[-6.92, 9.74]	[44.62, 52.29]	[-5.07, 5.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.33		48.98		48.20	
95% CI	[38.63, 56.02]		[38.89, 59.07]		[41.64, 54.76]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.34		2.24		2.31	
95% CI	[1.80, 2.87]		[1.67, 2.80]		[1.92, 2.70]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.9 (2.61)	-0.6 (3.36)	47.3 (2.30)	1.1 (3.22)	47.1 (1.73)	0.2 (2.33)
95% CI	[41.70, 52.05]	[-7.28, 6.05]	[42.76, 51.90]	[-5.34, 7.47]	[43.69, 50.53]	[-4.39, 4.82]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.48		46.26		46.89	
95% CI	[39.04, 55.93]		[38.39, 54.13]		[41.15, 52.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.39		2.61		2.51	
95% CI	[1.85, 2.93]		[2.03, 3.19]		[2.12, 2.91]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	24.3 (2.46)	24.6 (3.14)	24.2 (2.89)	23.8 (3.42)	24.3 (2.68)	24.2 (3.29)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	73.7 (20.96)	21.4 (5.58)	73.0 (18.27)	23.2 (5.94)	73.4 (19.56)	22.4 (5.79)
EAP						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	71.4 (18.73)	22.0 (5.21)	72.2 (19.38)	23.2 (5.49)	71.8 (18.99)	22.6 (5.35)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.3 (2.34)	-3.1 (3.41)	48.9 (1.99)	-0.7 (2.79)	49.1 (1.53)	-1.9 (2.18)
95% CI	[44.67, 54.00]	[-9.83, 3.73]	[44.90, 52.82]	[-6.25, 4.86]	[46.10, 52.13]	[-6.21, 2.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	52.39		49.55		51.01	
95% CI	[44.16, 60.62]		[42.73, 56.38]		[45.76, 56.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.95		3.21		3.09	
95% CI	[2.31, 3.58]		[2.57, 3.85]		[2.64, 3.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (2.10)	-2.6 (3.05)	48.1 (2.09)	-0.7 (2.95)	47.5 (1.47)	-1.7 (2.12)
95% CI	[42.82, 51.16]	[-8.62, 3.50]	[43.91, 52.21]	[-6.61, 5.14]	[44.63, 50.45]	[-5.84, 2.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.55		48.80		49.21	
95% CI	[42.19, 56.91]		[41.60, 55.99]		[44.12, 54.30]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.12		2.99		3.08	
95% CI	[2.46, 3.77]		[2.38, 3.61]		[2.63, 3.53]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.1.1.s9.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.8982		0.2085		0.2236	
Vist 13/ET	0.3161		0.1395		0.0561	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
EAP:n/N1 (%)	53/58 (91.4)	1/35 (2.9)	57/59 (96.6)	1/30 (3.3)	110/117 (94.0)	2/65 (3.1)
RR [95%-CI]; p-value	31.98 [4.63, 221.09], 0.0004		28.98 [4.22, 199.20], 0.0006		30.56 [7.80, 119.67], <0.0001	
OR [95%-CI]; p-value	360.40 [40.34, 3219.60], <0.0001		826.50 [71.91, 9498.89], <0.0001		495.00 [99.77, 2455.90], <0.0001	
RD [95%-CI]; p-value	0.89 [0.79, 0.98], <0.0001		0.93 [0.85, 1.00], <0.0001		0.91 [0.85, 0.97], <0.0001	
Vist 13/ET:n/N1 (%)	50/58 (86.2)	0/35 (0.0)	56/59 (94.9)	1/30 (3.3)	106/117 (90.6)	1/65 (1.5)
RR [95%-CI]; p-value	61.21 [3.90, 961.41], 0.0034		28.47 [4.14, 195.77], 0.0007		58.89 [8.41, 412.14], <0.0001	
OR [95%-CI]; p-value	437.50 [24.32, 7868.78], <0.0001		541.33 [53.89, 5438.18], <0.0001		616.73 [77.78, 4889.87], <0.0001	
RD [95%-CI]; p-value	0.85 [0.75, 0.94], <0.0001		0.92 [0.83, 1.00], <0.0001		0.89 [0.83, 0.95], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
EAP:n/N2 (%)	57/57 (100.0)	1/27 (3.7)	59/60 (98.3)	4/30 (13.3)	116/117 (99.1)	5/57 (8.8)
RR [95%-CI]; p-value	26.77 [3.91, 183.20], 0.0008		7.38 [2.96, 18.38], <0.0001		11.30 [4.89, 26.11], <0.0001	
OR [95%-CI]; p-value	2964.00 [96.35, 91180.21], <0.0001		383.50 [40.85, 3600.00], <0.0001		1206.40 [137.50, 10585.09], <0.0001	
RD [95%-CI]; p-value	0.95 [0.88, 1.00], <0.0001		0.85 [0.72, 0.98], <0.0001		0.90 [0.83, 0.98], <0.0001	
Vist 13/ET:n/N2 (%)	54/57 (94.7)	2/27 (7.4)	59/60 (98.3)	5/30 (16.7)	113/117 (96.6)	7/57 (12.3)
RR [95%-CI]; p-value	12.79 [3.37, 48.60], 0.0002		5.90 [2.65, 13.14], <0.0001		7.86 [3.93, 15.75], <0.0001	
OR [95%-CI]; p-value	225.00 [35.34, 1432.32], <0.0001		295.00 [32.77, 2655.44], <0.0001		201.79 [56.51, 720.53], <0.0001	
RD [95%-CI]; p-value	0.87 [0.76, 0.99], <0.0001		0.82 [0.68, 0.95], <0.0001		0.84 [0.75, 0.93], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_1_1_m_25d30_bl25d_pp.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalysen - Sicherheitsendpunkte Sicherheits-relevante sHPT-assoziierte Parameter (ITT-Population)

Folgende Daten werden für die ITT-Population

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum
- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.12.1.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7108		0.3837		0.7849	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	9.2 (0.30)	9.3 (0.26)	9.2 (0.36)	9.2 (0.32)	9.2 (0.33)	9.2 (0.29)
Visit 13/ET						
n/N1	57/59	30/30	47/50	28/32	104/109	58/62
Mean (SD)	9.5 (0.45)	9.3 (0.37)	9.5 (0.46)	9.4 (0.52)	9.5 (0.45)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.15, 0.36]	[-0.08, 0.20]	[0.19, 0.39]	[0.04, 0.30]	[0.20, 0.35]	[0.01, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.12		0.17	
95% CI	[0.02, 0.37]		[-0.04, 0.29]		[0.05, 0.29]	
p-value	0.0259		0.1405		0.0064	
Hedges' g	0.54		0.36		0.46	
95% CI	[0.09, 0.99]		[-0.11, 0.82]		[0.13, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_m_dca_age.sas using SAS 9.4

Table 12.4.12.1.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	9.2 (0.28)	9.2 (0.29)	9.3 (0.34)	9.3 (0.24)	9.2 (0.31)	9.3 (0.27)
Visit 13/ET						
n/N2	74/82	38/42	85/94	34/40	159/176	72/82
Mean (SD)	9.5 (0.54)	9.4 (0.28)	9.5 (0.37)	9.4 (0.57)	9.5 (0.46)	9.4 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.2 (0.06)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.23, 0.42]	[0.03, 0.28]	[0.20, 0.35]	[-0.07, 0.17]	[0.24, 0.36]	[0.02, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.22		0.19	
95% CI	[0.01, 0.33]		[0.08, 0.37]		[0.09, 0.30]	
p-value	0.0376		0.0029		0.0004	
Hedges' g	0.43		0.63		0.52	
95% CI	[0.04, 0.82]		[0.23, 1.03]		[0.23, 0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_m_dca_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3875		0.3834		0.9660	
Comparison Baseline vs. EAP	0.9715		0.4617		0.5618	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	3.8 (0.53)	4.0 (0.57)	3.9 (0.62)	3.8 (0.55)	3.8 (0.57)	3.9 (0.57)
Visit 13/ET						
n/N1	57/59	30/30	47/50	28/32	104/109	58/62
Mean (SD)	3.9 (0.67)	4.0 (0.70)	4.2 (0.92)	3.7 (0.88)	4.0 (0.80)	3.9 (0.81)
EAP						
n/N1	57/59	30/30	48/50	29/32	105/109	59/62
Mean (SD)	3.9 (0.55)	4.1 (0.53)	4.1 (0.80)	3.7 (0.65)	4.0 (0.68)	3.9 (0.61)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.11)	0.3 (0.11)	-0.0 (0.14)	0.2 (0.07)	0.0 (0.09)
95% CI	[-0.09, 0.22]	[-0.13, 0.30]	[0.11, 0.55]	[-0.32, 0.26]	[0.07, 0.33]	[-0.16, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.36		0.19	
95% CI	[-0.29, 0.24]		[-0.01, 0.73]		[-0.03, 0.40]	
p-value	0.8692		0.0534		0.0956	
Hedges' g	0.09		0.43		0.26	
95% CI	[-0.35, 0.52]		[-0.04, 0.90]		[-0.06, 0.58]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.1 (0.08)	0.3 (0.09)	-0.0 (0.11)	0.2 (0.05)	0.0 (0.07)
95% CI	[-0.00, 0.22]	[-0.04, 0.26]	[0.09, 0.44]	[-0.23, 0.22]	[0.09, 0.29]	[-0.09, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		0.28		0.15	
95% CI	[-0.19, 0.19]		[-0.01, 0.56]		[-0.02, 0.31]	
p-value	0.9976		0.0580		0.0795	
Hedges' g	0.16		0.38		0.28	
95% CI	[-0.28, 0.60]		[-0.08, 0.84]		[-0.04, 0.60]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	3.7 (0.55)	3.7 (0.57)	3.7 (0.53)	3.6 (0.39)	3.7 (0.54)	3.7 (0.49)
Visit 13/ET						
n/N2	74/82	38/42	85/94	34/40	159/176	72/82
Mean (SD)	3.9 (0.73)	3.8 (0.61)	3.9 (0.61)	3.7 (0.54)	3.9 (0.67)	3.8 (0.57)
EAP						
n/N2	74/82	39/42	88/94	36/40	162/176	75/82
Mean (SD)	3.9 (0.68)	3.8 (0.60)	3.9 (0.60)	3.8 (0.41)	3.9 (0.64)	3.8 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.07)	0.1 (0.09)	0.2 (0.05)	0.1 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.16, 0.41]	[-0.09, 0.27]	[0.09, 0.30]	[-0.08, 0.25]	[0.16, 0.32]	[-0.04, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.11		0.15	
95% CI	[-0.02, 0.42]		[-0.09, 0.31]		[0.01, 0.30]	
p-value	0.0789		0.2703		0.0425	
Hedges' g	0.34		0.16		0.25	
95% CI	[-0.05, 0.74]		[-0.24, 0.55]		[-0.03, 0.53]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.04)	0.1 (0.07)	0.2 (0.03)	0.1 (0.05)
95% CI	[0.11, 0.31]	[0.00, 0.28]	[0.13, 0.30]	[-0.01, 0.26]	[0.15, 0.28]	[0.04, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.06		0.09		0.07	
95% CI	[-0.11, 0.24]		[-0.07, 0.25]		[-0.04, 0.19]	
p-value	0.4691		0.2637		0.2130	
Hedges' g	0.15		0.16		0.16	
95% CI	[-0.23, 0.54]		[-0.23, 0.54]		[-0.12, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.5.1.1.1.s1
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8407		0.9975		0.9293	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	38/59	17/30	31/50	22/32	69/109	39/62
Mean (SD)	44.7 (34.47)	35.7 (19.86)	37.6 (29.38)	37.3 (32.34)	41.5 (32.25)	36.6 (27.29)
Visit 13/ET						
n/N1	33/59	13/30	30/50	15/32	63/109	28/62
Mean (SD)	49.5 (41.83)	54.7 (79.42)	72.4 (87.66)	62.6 (58.37)	60.4 (68.06)	58.9 (67.72)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	11.8 (10.21)	10.5 (16.31)	41.6 (19.99)	22.5 (27.62)	26.3 (10.66)	17.5 (15.75)
95% CI	[-8.86, 32.54]	[-22.56, 43.58]	[0.69, 82.46]	[-33.98, 79.00]	[5.06, 47.63]	[-13.94, 48.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.33		19.07		8.83	
95% CI	[-37.74, 40.39]		[-50.67, 88.80]		[-29.16, 46.82]	
p-value	0.9455		0.5803		0.6442	
Hedges' g	0.03		0.18		0.10	
95% CI	[-0.65, 0.72]		[-0.53, 0.90]		[-0.39, 0.60]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_5_1_1_m_fgf23_age.sas using SAS 9.4

Table 12.5.1.1.1.s1
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	59/82	24/42	53/94	25/40	112/176	49/82
Mean (SD)	48.8 (59.35)	51.2 (41.99)	33.3 (21.67)	34.4 (28.12)	41.5 (46.06)	42.6 (36.23)
Visit 13/ET						
n/N2	44/82	13/42	45/94	13/40	89/176	26/82
Mean (SD)	52.8 (54.95)	53.6 (29.37)	52.5 (51.22)	61.5 (55.49)	52.6 (52.79)	57.6 (43.69)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	4.0 (8.09)	2.6 (14.39)	25.4 (9.76)	20.3 (15.69)	13.6 (6.31)	12.4 (10.60)
95% CI	[-12.24, 20.25]	[-26.31, 31.47]	[5.74, 45.11]	[-11.32, 51.97]	[1.12, 26.18]	[-8.63, 33.45]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.42		5.10		1.24	
95% CI	[-31.75, 34.59]		[-32.48, 42.68]		[-23.30, 25.78]	
p-value	0.9317		0.7856		0.9206	
Hedges' g	0.13		0.18		0.13	
95% CI	[-0.49, 0.74]		[-0.45, 0.82]		[-0.31, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_5_1_1_m_fgf23_age.sas using SAS 9.4

Table 12.4.12.1.2.s1
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5198		0.8698		0.7350	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	49/50	32/32	108/109	62/62
Mean (SD)	29.1 (12.94)	31.2 (10.57)	30.1 (10.80)	31.1 (10.23)	29.5 (11.97)	31.1 (10.31)
Visit 13/ET						
n/N1	57/59	30/30	47/50	28/32	104/109	58/62
Mean (SD)	28.9 (12.41)	31.1 (12.07)	29.4 (13.58)	30.0 (10.92)	29.2 (12.89)	30.6 (11.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.7 (0.89)	0.0 (1.23)	-0.6 (1.04)	-0.7 (1.34)	-0.6 (0.68)	-0.3 (0.91)
95% CI	[-2.49, 1.06]	[-2.42, 2.47]	[-2.62, 1.52]	[-3.36, 2.00]	[-1.98, 0.72]	[-2.14, 1.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.74		0.13		-0.29	
95% CI	[-3.77, 2.28]		[-3.25, 3.52]		[-2.55, 1.96]	
p-value	0.6257		0.9383		0.7988	
Hedges' g	-0.07		0.02		-0.03	
95% CI	[-0.51, 0.37]		[-0.45, 0.48]		[-0.35, 0.29]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_2_m_egfr_age.sas using SAS 9.4

Table 12.4.12.1.2.s1
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	31.2 (9.49)	33.1 (11.39)	31.4 (9.47)	32.3 (9.18)	31.3 (9.45)	32.7 (10.31)
Visit 13/ET						
n/N2	74/82	38/42	85/94	34/40	159/176	72/82
Mean (SD)	30.5 (11.43)	32.7 (10.83)	29.5 (10.28)	30.6 (10.43)	29.9 (10.81)	31.8 (10.62)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.3 (0.85)	-0.7 (1.20)	-1.8 (0.57)	-1.6 (0.90)	-1.0 (0.51)	-1.2 (0.75)
95% CI	[-1.94, 1.44]	[-3.07, 1.67]	[-2.97, -0.71]	[-3.40, 0.18]	[-2.02, -0.03]	[-2.67, 0.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.45		-0.23		0.16	
95% CI	[-2.48, 3.37]		[-2.34, 1.89]		[-1.63, 1.95]	
p-value	0.7625		0.8332		0.8610	
Hedges' g	0.12		-0.03		0.04	
95% CI	[-0.27, 0.51]		[-0.43, 0.36]		[-0.23, 0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_2_m_egfr_age.sas using SAS 9.4

Table 12.4.15.1.1.s1
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0364		0.1948		0.0218	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	49/59	24/30	42/50	26/32	91/109	50/62
Mean (SD)	0.6 (0.68)	0.7 (0.68)	0.8 (1.04)	1.2 (1.45)	0.7 (0.87)	1.0 (1.16)
Visit 13/ET						
n/N1	48/59	26/30	40/50	22/32	88/109	48/62
Mean (SD)	0.5 (0.54)	0.8 (0.98)	0.9 (1.11)	1.2 (2.14)	0.7 (0.86)	1.0 (1.61)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.08)	0.2 (0.11)	0.1 (0.18)	0.3 (0.24)	-0.0 (0.09)	0.2 (0.13)
95% CI	[-0.25, 0.07]	[-0.06, 0.37]	[-0.29, 0.45]	[-0.14, 0.84]	[-0.19, 0.18]	[-0.00, 0.50]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.24		-0.27		-0.25	
95% CI	[-0.51, 0.02]		[-0.88, 0.34]		[-0.56, 0.06]	
p-value	0.0725		0.3845		0.1183	
Hedges' g	-0.38		-0.23		-0.28	
95% CI	[-0.85, 0.10]		[-0.75, 0.29]		[-0.63, 0.08]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_15_1_1_m_ua_age.sas using SAS 9.4

Table 12.4.15.1.1.s1
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	67/82	38/42	68/94	29/40	135/176	67/82
Mean (SD)	0.6 (0.82)	0.6 (1.02)	0.7 (1.03)	0.6 (0.88)	0.7 (0.93)	0.6 (0.95)
Visit 13/ET						
n/N2	57/82	34/42	57/94	21/40	114/176	55/82
Mean (SD)	0.9 (1.39)	0.5 (0.76)	0.9 (1.45)	0.6 (0.78)	0.9 (1.41)	0.5 (0.76)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.11)	-0.1 (0.15)	0.2 (0.11)	-0.0 (0.18)	0.2 (0.08)	-0.1 (0.12)
95% CI	[-0.02, 0.42]	[-0.36, 0.22]	[-0.05, 0.39]	[-0.40, 0.33]	[0.03, 0.34]	[-0.28, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.27		0.20		0.24	
95% CI	[-0.10, 0.64]		[-0.22, 0.63]		[-0.04, 0.52]	
p-value	0.1454		0.3437		0.0955	
Hedges' g	0.31		0.25		0.29	
95% CI	[-0.12, 0.74]		[-0.26, 0.76]		[-0.04, 0.61]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_15_1_1_m_ua_age.sas using SAS 9.4

Table 12.4.12.1.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8698		0.3710		0.4986	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	9.2 (0.29)	9.2 (0.24)	9.3 (0.33)	9.3 (0.26)	9.3 (0.32)	9.3 (0.25)
Visit 13/ET						
n/N1	66/71	32/33	65/71	32/39	131/142	64/72
Mean (SD)	9.5 (0.47)	9.4 (0.34)	9.6 (0.37)	9.5 (0.59)	9.6 (0.43)	9.4 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.05)	0.1 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.20, 0.38]	[0.00, 0.26]	[0.19, 0.38]	[0.00, 0.27]	[0.22, 0.35]	[0.04, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.16		0.15		0.15	
95% CI	[0.01, 0.32]		[-0.02, 0.31]		[0.04, 0.26]	
p-value	0.0428		0.0781		0.0074	
Hedges' g	0.45		0.38		0.42	
95% CI	[0.03, 0.87]		[-0.04, 0.80]		[0.12, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_1_m_dca_sex.sas using SAS 9.4

Table 12.4.12.1.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	9.2 (0.28)	9.2 (0.31)	9.2 (0.34)	9.2 (0.29)	9.2 (0.31)	9.2 (0.30)
Visit 13/ET						
n/N2	65/70	36/39	67/73	30/33	132/143	66/72
Mean (SD)	9.5 (0.53)	9.3 (0.30)	9.4 (0.41)	9.2 (0.45)	9.4 (0.47)	9.3 (0.38)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.19, 0.40]	[-0.04, 0.24]	[0.20, 0.36]	[-0.06, 0.18]	[0.23, 0.36]	[-0.01, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.22		0.21	
95% CI	[0.02, 0.37]		[0.08, 0.37]		[0.10, 0.32]	
p-value	0.0304		0.0032		0.0003	
Hedges' g	0.50		0.66		0.56	
95% CI	[0.09, 0.91]		[0.22, 1.09]		[0.26, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_1_m_dca_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0292		0.1518		0.6219	
Comparison Baseline vs. EAP	0.1144		0.2284		0.8782	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	3.8 (0.54)	3.9 (0.60)	3.8 (0.42)	3.8 (0.44)	3.8 (0.48)	3.8 (0.52)
Visit 13/ET						
n/N1	66/71	32/33	65/71	32/39	131/142	64/72
Mean (SD)	4.0 (0.66)	3.8 (0.61)	4.0 (0.57)	3.9 (0.72)	4.0 (0.62)	3.8 (0.66)
EAP						
n/N1	66/71	33/33	68/71	33/39	134/142	66/72
Mean (SD)	4.0 (0.62)	4.0 (0.56)	4.0 (0.47)	3.9 (0.55)	4.0 (0.55)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	-0.0 (0.09)	0.1 (0.07)	0.1 (0.09)	0.2 (0.04)	0.0 (0.06)
95% CI	[0.12, 0.37]	[-0.22, 0.13]	[0.01, 0.26]	[-0.09, 0.28]	[0.10, 0.28]	[-0.10, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.29		0.04		0.17	
95% CI	[0.08, 0.51]		[-0.19, 0.26]		[0.01, 0.32]	
p-value	0.0079		0.7374		0.0335	
Hedges' g	0.61		0.04		0.32	
95% CI	[0.18, 1.04]		[-0.38, 0.46]		[0.02, 0.62]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.06)	0.1 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.05)
95% CI	[0.14, 0.32]	[-0.04, 0.22]	[0.06, 0.24]	[-0.02, 0.23]	[0.13, 0.25]	[0.01, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.15		0.04		0.09	
95% CI	[-0.01, 0.30]		[-0.12, 0.20]		[-0.02, 0.20]	
p-value	0.0690		0.6020		0.1076	
Hedges' g	0.43		0.06		0.24	
95% CI	[0.01, 0.85]		[-0.35, 0.47]		[-0.05, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	3.6 (0.55)	3.7 (0.57)	3.7 (0.67)	3.6 (0.49)	3.7 (0.61)	3.7 (0.54)
Visit 13/ET						
n/N2	65/70	36/39	67/73	30/33	132/143	66/72
Mean (SD)	3.8 (0.73)	3.9 (0.71)	4.1 (0.88)	3.6 (0.68)	3.9 (0.82)	3.8 (0.71)
EAP						
n/N2	65/70	36/39	68/73	32/33	133/143	68/72
Mean (SD)	3.8 (0.60)	3.9 (0.60)	4.0 (0.85)	3.7 (0.49)	3.9 (0.75)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.2 (0.11)	0.3 (0.08)	-0.0 (0.13)	0.2 (0.06)	0.1 (0.08)
95% CI	[-0.02, 0.29]	[-0.01, 0.41]	[0.18, 0.51]	[-0.29, 0.21]	[0.13, 0.35]	[-0.08, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.07		0.38		0.16	
95% CI	[-0.33, 0.19]		[0.08, 0.68]		[-0.04, 0.36]	
p-value	0.5879		0.0133		0.1073	
Hedges' g	-0.04		0.48		0.22	
95% CI	[-0.45, 0.36]		[0.05, 0.92]		[-0.08, 0.51]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.3 (0.07)	0.0 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[-0.02, 0.21]	[-0.00, 0.31]	[0.18, 0.46]	[-0.17, 0.24]	[0.12, 0.30]	[-0.04, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.06		0.29		0.12	
95% CI	[-0.25, 0.14]		[0.04, 0.54]		[-0.03, 0.28]	
p-value	0.5561		0.0230		0.1244	
Hedges' g	-0.04		0.42		0.21	
95% CI	[-0.44, 0.37]		[0.00, 0.85]		[-0.08, 0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.5.1.1.1.s2
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4258		0.1982		0.1099	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	40/71	19/33	38/71	26/39	78/142	45/72
Mean (SD)	46.4 (38.38)	39.2 (36.40)	32.1 (21.10)	35.9 (32.33)	39.5 (31.80)	37.3 (33.74)
Visit 13/ET						
n/N1	36/71	7/33	33/71	15/39	69/142	22/72
Mean (SD)	48.5 (43.08)	71.6 (105.49)	52.1 (51.91)	73.1 (52.84)	50.2 (47.19)	72.6 (71.00)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	11.2 (10.32)	28.4 (22.14)	19.1 (11.20)	33.6 (15.54)	15.1 (7.64)	30.9 (13.33)
95% CI	[-9.72, 32.15]	[-16.54, 73.27]	[-3.72, 41.92]	[1.97, 65.27]	[-0.13, 30.37]	[4.29, 57.48]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-17.15		-14.52		-15.77	
95% CI	[-66.77, 32.47]		[-53.64, 24.60]		[-46.48, 14.95]	
p-value	0.4878		0.4551		0.3094	
Hedges' g	-0.23		-0.23		-0.26	
95% CI	[-1.03, 0.57]		[-0.91, 0.45]		[-0.78, 0.26]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_5_1_1_1_m_fgf23_sex.sas using SAS 9.4

Table 12.5.1.1.1.s2
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	57/70	22/39	46/73	21/33	103/143	43/72
Mean (SD)	47.8 (58.43)	49.5 (34.04)	37.2 (27.36)	35.6 (27.31)	43.1 (47.25)	42.7 (31.37)
Visit 13/ET						
n/N2	41/70	19/39	42/73	13/33	83/143	32/72
Mean (SD)	53.9 (54.89)	47.7 (30.16)	67.0 (78.88)	49.4 (58.92)	60.5 (68.01)	48.4 (43.27)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	4.6 (8.21)	-4.8 (12.11)	40.0 (14.90)	11.6 (24.01)	21.7 (8.07)	2.3 (12.49)
95% CI	[-11.92, 21.04]	[-29.10, 19.54]	[9.92, 70.17]	[-36.88, 60.16]	[5.73, 37.77]	[-22.46, 27.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	9.34		28.41		19.40	
95% CI	[-20.05, 38.72]		[-28.81, 85.62]		[-10.14, 48.95]	
p-value	0.5263		0.3217		0.1954	
Hedges' g	0.17		0.39		0.29	
95% CI	[-0.40, 0.74]		[-0.27, 1.05]		[-0.14, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_5_1_1_1_m_fgf23_sex.sas using SAS 9.4

Table 12.4.12.1.2.s2
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6570		0.5868		0.4980	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	70/71	39/39	141/142	72/72
Mean (SD)	29.9 (10.81)	32.0 (11.56)	31.9 (10.52)	32.5 (10.19)	30.9 (10.68)	32.3 (10.76)
Visit 13/ET						
n/N1	66/71	32/33	65/71	32/39	131/142	64/72
Mean (SD)	30.1 (11.76)	32.2 (11.68)	31.3 (13.12)	32.1 (11.00)	30.7 (12.42)	32.1 (11.26)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.78)	-0.1 (1.12)	-0.7 (0.81)	-1.1 (1.16)	-0.2 (0.56)	-0.6 (0.81)
95% CI	[-1.18, 1.91]	[-2.29, 2.17]	[-2.32, 0.90]	[-3.38, 1.21]	[-1.27, 0.95]	[-2.20, 0.99]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.43		0.37		0.44	
95% CI	[-2.29, 3.15]		[-2.43, 3.18]		[-1.50, 2.39]	
p-value	0.7562		0.7935		0.6547	
Hedges' g	0.11		0.05		0.08	
95% CI	[-0.31, 0.53]		[-0.37, 0.47]		[-0.22, 0.38]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_2_m_egfr_sex.sas using SAS 9.4

Table 12.4.12.1.2.s2
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	30.7 (11.38)	32.6 (10.68)	30.0 (9.30)	30.9 (8.95)	30.4 (10.34)	31.8 (9.90)
Visit 13/ET						
n/N2	65/70	36/39	67/73	30/33	132/143	66/72
Mean (SD)	29.5 (12.01)	31.9 (11.19)	27.6 (9.45)	28.5 (9.92)	28.5 (10.78)	30.3 (10.69)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.3 (0.95)	-0.7 (1.28)	-2.0 (0.66)	-1.3 (0.99)	-1.6 (0.58)	-1.0 (0.82)
95% CI	[-3.16, 0.61]	[-3.21, 1.86]	[-3.32, -0.69]	[-3.31, 0.62]	[-2.77, -0.49]	[-2.65, 0.59]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.60		-0.66		-0.60	
95% CI	[-3.77, 2.57]		[-3.02, 1.70]		[-2.59, 1.38]	
p-value	0.7085		0.5808		0.5495	
Hedges' g	-0.02		-0.11		-0.06	
95% CI	[-0.43, 0.38]		[-0.54, 0.31]		[-0.36, 0.23]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_2_m_egfr_sex.sas using SAS 9.4

Table 12.4.15.1.1.s2
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2665		0.7542		0.5608	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	57/71	24/33	47/71	26/39	104/142	50/72
Mean (SD)	0.5 (0.81)	0.6 (0.66)	0.6 (0.81)	0.7 (0.97)	0.6 (0.81)	0.7 (0.83)
Visit 13/ET						
n/N1	50/71	25/33	40/71	17/39	90/142	42/72
Mean (SD)	0.6 (1.08)	0.6 (0.78)	0.5 (0.72)	0.6 (0.72)	0.6 (0.93)	0.6 (0.75)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.10)	0.1 (0.14)	-0.0 (0.10)	-0.0 (0.16)	-0.0 (0.08)	0.0 (0.11)
95% CI	[-0.20, 0.19]	[-0.18, 0.38]	[-0.26, 0.16]	[-0.36, 0.28]	[-0.17, 0.13]	[-0.21, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.10		-0.01		-0.04	
95% CI	[-0.45, 0.24]		[-0.39, 0.37]		[-0.31, 0.23]	
p-value	0.5525		0.9638		0.7845	
Hedges' g	-0.15		0.05		-0.06	
95% CI	[-0.64, 0.33]		[-0.52, 0.63]		[-0.44, 0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_15_1_1_m_ua_sex.sas using SAS 9.4

Table 12.4.15.1.1.s2
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	59/70	38/39	63/73	29/33	122/143	67/72
Mean (SD)	0.7 (0.72)	0.7 (1.02)	0.9 (1.16)	1.0 (1.39)	0.8 (0.97)	0.8 (1.20)
Visit 13/ET						
n/N2	55/70	35/39	57/73	26/33	112/143	61/72
Mean (SD)	0.8 (1.11)	0.7 (0.94)	1.2 (1.56)	1.1 (2.01)	1.0 (1.36)	0.9 (1.49)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	-0.0 (0.13)	0.2 (0.14)	0.3 (0.20)	0.2 (0.09)	0.1 (0.12)
95% CI	[-0.07, 0.35]	[-0.29, 0.23]	[-0.04, 0.52]	[-0.07, 0.74]	[0.02, 0.36]	[-0.09, 0.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		-0.10		0.04	
95% CI	[-0.16, 0.50]		[-0.59, 0.39]		[-0.25, 0.34]	
p-value	0.3118		0.6974		0.7702	
Hedges' g	0.21		-0.07		0.08	
95% CI	[-0.21, 0.63]		[-0.53, 0.40]		[-0.23, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_15_1_1_m_ua_sex.sas using SAS 9.4

Table 12.4.12.1.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5708		0.0714		0.4559	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	9.2 (0.28)	9.2 (0.27)	9.3 (0.33)	9.3 (0.26)	9.2 (0.31)	9.2 (0.26)
Visit 13/ET						
n/N1	67/73	33/36	72/77	26/29	139/150	59/65
Mean (SD)	9.4 (0.47)	9.3 (0.31)	9.5 (0.41)	9.4 (0.56)	9.5 (0.44)	9.4 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.04)	0.2 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.18, 0.36]	[-0.05, 0.20]	[0.17, 0.34]	[0.03, 0.32]	[0.20, 0.32]	[0.03, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.08		0.14	
95% CI	[0.03, 0.35]		[-0.09, 0.25]		[0.03, 0.25]	
p-value	0.0177		0.3382		0.0163	
Hedges' g	0.57		0.21		0.41	
95% CI	[0.15, 0.99]		[-0.23, 0.66]		[0.11, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_1_m_dca_wt.sas using SAS 9.4

Table 12.4.12.1.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	9.2 (0.29)	9.2 (0.29)	9.2 (0.37)	9.3 (0.30)	9.2 (0.33)	9.2 (0.30)
Visit 13/ET						
n/N2	64/68	35/36	60/67	36/43	124/135	71/79
Mean (SD)	9.6 (0.53)	9.4 (0.34)	9.5 (0.39)	9.3 (0.53)	9.5 (0.47)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.2 (0.07)	0.3 (0.04)	0.0 (0.06)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.22, 0.43]	[0.01, 0.29]	[0.23, 0.40]	[-0.07, 0.16]	[0.25, 0.39]	[0.01, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.27		0.22	
95% CI	[-0.00, 0.34]		[0.12, 0.41]		[0.11, 0.33]	
p-value	0.0545		0.0004		0.0002	
Hedges' g	0.40		0.78		0.57	
95% CI	[-0.01, 0.82]		[0.35, 1.20]		[0.28, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_1_m_dca_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4071		0.7514		0.4573	
Comparison Baseline vs. EAP	0.2317		0.4194		0.1839	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	3.8 (0.59)	3.9 (0.61)	3.8 (0.56)	3.7 (0.47)	3.8 (0.58)	3.8 (0.55)
Visit 13/ET						
n/N1	67/73	33/36	72/77	26/29	139/150	59/65
Mean (SD)	4.0 (0.79)	3.9 (0.55)	4.0 (0.67)	3.6 (0.62)	4.0 (0.73)	3.8 (0.60)
EAP						
n/N1	67/73	34/36	73/77	26/29	140/150	60/65
Mean (SD)	4.0 (0.70)	4.0 (0.50)	4.0 (0.66)	3.6 (0.51)	4.0 (0.68)	3.8 (0.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.07)	0.1 (0.10)	0.2 (0.07)	-0.1 (0.11)	0.2 (0.05)	-0.0 (0.08)
95% CI	[0.13, 0.41]	[-0.12, 0.29]	[0.05, 0.32]	[-0.35, 0.10]	[0.13, 0.32]	[-0.17, 0.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.31		0.24	
95% CI	[-0.07, 0.43]		[0.05, 0.58]		[0.06, 0.42]	
p-value	0.1499		0.0222		0.0094	
Hedges' g	0.35		0.38		0.35	
95% CI	[-0.07, 0.76]		[-0.07, 0.83]		[0.04, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.2 (0.06)	-0.1 (0.10)	0.2 (0.04)	0.0 (0.06)
95% CI	[0.15, 0.35]	[-0.02, 0.27]	[0.08, 0.31]	[-0.30, 0.09]	[0.14, 0.30]	[-0.10, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.30		0.20	
95% CI	[-0.06, 0.30]		[0.07, 0.53]		[0.06, 0.34]	
p-value	0.1816		0.0119		0.0061	
Hedges' g	0.33		0.45		0.37	
95% CI	[-0.08, 0.74]		[0.00, 0.90]		[0.06, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	3.7 (0.49)	3.8 (0.57)	3.7 (0.55)	3.7 (0.47)	3.7 (0.52)	3.7 (0.52)
Visit 13/ET						
n/N2	64/68	35/36	60/67	36/43	124/135	71/79
Mean (SD)	3.8 (0.59)	3.8 (0.76)	4.0 (0.82)	3.8 (0.76)	3.9 (0.72)	3.8 (0.75)
EAP						
n/N2	64/68	35/36	63/67	39/43	127/135	74/79
Mean (SD)	3.8 (0.51)	3.9 (0.65)	4.0 (0.72)	3.9 (0.53)	3.9 (0.63)	3.9 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.1 (0.09)	0.3 (0.08)	0.1 (0.11)	0.2 (0.05)	0.1 (0.07)
95% CI	[-0.03, 0.25]	[-0.10, 0.27]	[0.15, 0.48]	[-0.07, 0.35]	[0.11, 0.32]	[-0.03, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.18		0.11	
95% CI	[-0.21, 0.26]		[-0.09, 0.44]		[-0.07, 0.28]	
p-value	0.8469		0.1835		0.2299	
Hedges' g	0.10		0.28		0.19	
95% CI	[-0.31, 0.51]		[-0.13, 0.69]		[-0.10, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.3 (0.06)	0.2 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[-0.03, 0.18]	[-0.02, 0.26]	[0.17, 0.40]	[0.03, 0.33]	[0.10, 0.26]	[0.05, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.10		0.03	
95% CI	[-0.22, 0.14]		[-0.09, 0.29]		[-0.09, 0.16]	
p-value	0.6470		0.2962		0.5985	
Hedges' g	-0.02		0.20		0.09	
95% CI	[-0.43, 0.39]		[-0.19, 0.60]		[-0.20, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.5.1.1.1.s3
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0913		0.7373		0.3450	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	46/73	20/36	42/77	22/29	88/150	42/65
Mean (SD)	36.0 (23.68)	39.7 (34.56)	37.4 (28.91)	35.2 (31.01)	36.7 (26.16)	37.3 (32.42)
Visit 13/ET						
n/N1	40/73	9/36	43/77	9/29	83/150	18/65
Mean (SD)	53.1 (58.81)	40.7 (27.24)	56.6 (54.41)	72.0 (63.58)	54.9 (56.25)	56.4 (50.11)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	22.1 (9.79)	-10.2 (22.35)	22.1 (11.89)	30.6 (22.99)	21.9 (7.63)	11.8 (15.98)
95% CI	[2.27, 41.89]	[-55.39, 35.08]	[-2.08, 46.23]	[-16.09, 77.37]	[6.73, 37.12]	[-20.06, 43.63]
Diff in LS-Mean [ER-Calcifediol - Placebo]	32.23		-8.56		10.14	
95% CI	[-17.88, 82.34]		[-61.66, 44.54]		[-25.53, 45.81]	
p-value	0.2007		0.7451		0.5729	
Hedges' g	0.65		0.09		0.33	
95% CI	[-0.16, 1.46]		[-0.68, 0.85]		[-0.23, 0.89]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_5_1_1_1_m_fgf23_wt.sas using SAS 9.4

Table 12.5.1.1.1.s3
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	51/68	21/36	42/67	25/43	93/135	46/79
Mean (SD)	57.4 (65.17)	49.6 (35.74)	32.4 (19.69)	36.2 (29.46)	46.1 (51.35)	42.3 (32.81)
Visit 13/ET						
n/N2	37/68	17/36	32/67	19/43	69/135	36/79
Mean (SD)	49.5 (37.60)	61.2 (69.66)	65.6 (84.18)	57.4 (53.24)	57.0 (63.60)	59.2 (60.66)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-4.4 (8.51)	7.0 (12.22)	40.7 (16.13)	20.1 (20.17)	17.2 (8.51)	12.7 (11.33)
95% CI	[-21.48, 12.74]	[-17.59, 31.50]	[8.03, 73.35]	[-20.74, 60.92]	[0.31, 34.15]	[-9.80, 35.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-11.32		20.60		4.52	
95% CI	[-41.25, 18.60]		[-31.69, 72.89]		[-23.64, 32.68]	
p-value	0.4506		0.4301		0.7506	
Hedges' g	-0.20		0.26		-0.01	
95% CI	[-0.77, 0.37]		[-0.36, 0.87]		[-0.43, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_5_1_1_1_m_fgf23_wt.sas using SAS 9.4

Table 12.4.12.1.2.s3
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3905		0.2142		0.1347	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	30.7 (11.02)	31.4 (11.76)	30.0 (9.61)	29.3 (8.97)	30.4 (10.29)	30.4 (10.58)
Visit 13/ET						
n/N1	67/73	33/36	72/77	26/29	139/150	59/65
Mean (SD)	29.1 (11.20)	31.8 (11.67)	28.1 (9.89)	29.0 (9.11)	28.6 (10.51)	30.6 (10.62)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.3 (0.74)	-0.4 (1.06)	-2.0 (0.59)	-0.8 (0.98)	-1.6 (0.47)	-0.6 (0.73)
95% CI	[-2.75, 0.20]	[-2.46, 1.75]	[-3.15, -0.82]	[-2.70, 1.18]	[-2.56, -0.70]	[-2.00, 0.87]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.92		-1.23		-1.06	
95% CI	[-3.50, 1.65]		[-3.49, 1.03]		[-2.77, 0.65]	
p-value	0.4794		0.2836		0.2217	
Hedges' g	-0.10		-0.25		-0.17	
95% CI	[-0.51, 0.31]		[-0.69, 0.20]		[-0.48, 0.13]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_2_m_egfr_wt.sas using SAS 9.4

Table 12.4.12.1.2.s3
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	66/67	43/43	134/135	79/79
Mean (SD)	29.9 (11.18)	33.3 (10.30)	32.1 (10.25)	33.4 (9.76)	31.0 (10.75)	33.4 (9.95)
Visit 13/ET						
n/N2	64/68	35/36	60/67	36/43	124/135	71/79
Mean (SD)	30.6 (12.52)	32.2 (11.18)	31.1 (13.11)	31.3 (11.54)	30.8 (12.76)	31.8 (11.29)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.99)	-0.4 (1.34)	-0.6 (0.89)	-1.6 (1.14)	-0.1 (0.67)	-1.0 (0.89)
95% CI	[-1.56, 2.36]	[-3.05, 2.27]	[-2.35, 1.16]	[-3.86, 0.68]	[-1.40, 1.25]	[-2.79, 0.71]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.80		1.00		0.97	
95% CI	[-2.52, 4.11]		[-1.88, 3.87]		[-1.23, 3.16]	
p-value	0.6345		0.4920		0.3872	
Hedges' g	0.15		0.14		0.15	
95% CI	[-0.25, 0.56]		[-0.27, 0.55]		[-0.14, 0.44]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_2_m_egfr_wt.sas using SAS 9.4

Table 12.4.15.1.1.s3
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9645		0.0707		0.1800	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	62/73	32/36	59/77	24/29	121/150	56/65
Mean (SD)	0.6 (0.74)	0.6 (0.69)	0.7 (1.09)	0.7 (0.97)	0.7 (0.92)	0.7 (0.81)
Visit 13/ET						
n/N1	57/73	30/36	53/77	21/29	110/150	51/65
Mean (SD)	0.8 (1.30)	0.6 (0.88)	0.9 (1.42)	1.1 (2.02)	0.8 (1.35)	0.8 (1.46)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.11)	0.1 (0.15)	0.1 (0.14)	0.5 (0.22)	0.1 (0.09)	0.3 (0.13)
95% CI	[-0.09, 0.34]	[-0.20, 0.40]	[-0.19, 0.38]	[0.04, 0.92]	[-0.07, 0.28]	[0.03, 0.55]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		-0.39		-0.18	
95% CI	[-0.34, 0.39]		[-0.92, 0.14]		[-0.49, 0.13]	
p-value	0.8897		0.1470		0.2495	
Hedges' g	0.06		-0.34		-0.13	
95% CI	[-0.38, 0.50]		[-0.85, 0.16]		[-0.46, 0.20]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_15_1_1_m_ua_wt.sas using SAS 9.4

Table 12.4.15.1.1.s3
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	54/68	30/36	51/67	31/43	105/135	61/79
Mean (SD)	0.6 (0.80)	0.7 (1.09)	0.8 (0.98)	1.0 (1.37)	0.7 (0.89)	0.9 (1.24)
Visit 13/ET						
n/N2	48/68	30/36	44/67	22/43	92/135	52/79
Mean (SD)	0.6 (0.80)	0.7 (0.87)	0.9 (1.20)	0.7 (1.17)	0.8 (1.02)	0.7 (1.00)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.08)	-0.0 (0.10)	0.2 (0.13)	-0.1 (0.19)	0.1 (0.08)	-0.1 (0.10)
95% CI	[-0.19, 0.14]	[-0.23, 0.18]	[-0.10, 0.43]	[-0.49, 0.27]	[-0.08, 0.22]	[-0.27, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		0.27		0.13	
95% CI	[-0.26, 0.26]		[-0.19, 0.74]		[-0.12, 0.39]	
p-value	0.9890		0.2455		0.2930	
Hedges' g	0.04		0.33		0.20	
95% CI	[-0.41, 0.50]		[-0.19, 0.85]		[-0.15, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_15_1_1_m_ua_wt.sas using SAS 9.4

Table 12.4.12.1.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5197		0.0048		0.0197	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	9.2 (0.28)	9.2 (0.30)	9.2 (0.33)	9.3 (0.27)	9.2 (0.31)	9.2 (0.29)
Visit 13/ET						
n/N1	78/85	45/48	90/98	40/46	168/183	85/94
Mean (SD)	9.5 (0.54)	9.3 (0.36)	9.6 (0.39)	9.3 (0.53)	9.5 (0.47)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.06)	0.3 (0.04)	0.0 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.24, 0.42]	[-0.01, 0.23]	[0.26, 0.41]	[-0.07, 0.15]	[0.27, 0.39]	[-0.01, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.22		0.29		0.26	
95% CI	[0.07, 0.38]		[0.16, 0.42]		[0.16, 0.36]	
p-value	0.0040		<0.0001		<0.0001	
Hedges' g	0.56		0.82		0.68	
95% CI	[0.18, 0.93]		[0.44, 1.21]		[0.41, 0.94]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_1_m_dca_race.sas using SAS 9.4

Table 12.4.12.1.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	9.2 (0.29)	9.3 (0.24)	9.3 (0.37)	9.3 (0.30)	9.3 (0.33)	9.3 (0.27)
Visit 13/ET						
n/N2	53/56	23/24	42/46	22/26	95/102	45/50
Mean (SD)	9.5 (0.44)	9.4 (0.23)	9.4 (0.41)	9.5 (0.55)	9.4 (0.42)	9.4 (0.42)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.2 (0.07)	0.2 (0.04)	0.2 (0.05)
95% CI	[0.14, 0.33]	[-0.01, 0.29]	[0.07, 0.28]	[0.06, 0.36]	[0.14, 0.28]	[0.06, 0.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.03		0.04	
95% CI	[-0.08, 0.28]		[-0.22, 0.15]		[-0.09, 0.17]	
p-value	0.2804		0.7165		0.5341	
Hedges' g	0.35		-0.10		0.15	
95% CI	[-0.13, 0.84]		[-0.61, 0.41]		[-0.20, 0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_1_m_dca_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9246		0.0652		0.1571	
Comparison Baseline vs. EAP	0.9774		0.1061		0.2086	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	3.7 (0.57)	3.8 (0.61)	3.8 (0.54)	3.7 (0.41)	3.7 (0.55)	3.8 (0.52)
Visit 13/ET						
n/N1	78/85	45/48	90/98	40/46	168/183	85/94
Mean (SD)	4.0 (0.71)	3.9 (0.72)	4.0 (0.76)	3.6 (0.67)	4.0 (0.74)	3.8 (0.71)
EAP						
n/N1	78/85	45/48	93/98	40/46	171/183	85/94
Mean (SD)	3.9 (0.64)	4.0 (0.63)	4.0 (0.69)	3.7 (0.50)	4.0 (0.67)	3.8 (0.59)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.09)	0.3 (0.06)	-0.0 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.07, 0.34]	[-0.09, 0.27]	[0.16, 0.41]	[-0.24, 0.14]	[0.16, 0.34]	[-0.11, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.33		0.23	
95% CI	[-0.11, 0.34]		[0.10, 0.56]		[0.07, 0.39]	
p-value	0.3239		0.0051		0.0048	
Hedges' g	0.24		0.50		0.37	
95% CI	[-0.13, 0.61]		[0.13, 0.88]		[0.11, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.05)	0.0 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.07, 0.27]	[-0.01, 0.26]	[0.17, 0.36]	[-0.13, 0.17]	[0.15, 0.29]	[-0.03, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.24		0.15	
95% CI	[-0.12, 0.22]		[0.06, 0.42]		[0.03, 0.27]	
p-value	0.5866		0.0079		0.0156	
Hedges' g	0.16		0.47		0.32	
95% CI	[-0.21, 0.53]		[0.10, 0.85]		[0.06, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	3.7 (0.50)	3.8 (0.56)	3.8 (0.62)	3.7 (0.57)	3.7 (0.56)	3.7 (0.56)
Visit 13/ET						
n/N2	53/56	23/24	42/46	22/26	95/102	45/50
Mean (SD)	3.9 (0.70)	3.8 (0.54)	3.9 (0.70)	3.9 (0.76)	3.9 (0.70)	3.9 (0.65)
EAP						
n/N2	53/56	24/24	43/46	25/26	96/102	49/50
Mean (SD)	3.9 (0.60)	3.9 (0.48)	4.0 (0.67)	3.9 (0.56)	3.9 (0.63)	3.9 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.11)	0.1 (0.09)	0.2 (0.13)	0.2 (0.06)	0.1 (0.08)
95% CI	[0.02, 0.31]	[-0.15, 0.29]	[-0.04, 0.33]	[-0.08, 0.44]	[0.04, 0.27]	[-0.04, 0.29]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.03		0.03	
95% CI	[-0.16, 0.37]		[-0.35, 0.29]		[-0.17, 0.23]	
p-value	0.4436		0.8337		0.7607	
Hedges' g	0.21		-0.09		0.05	
95% CI	[-0.27, 0.70]		[-0.60, 0.42]		[-0.30, 0.41]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.08)	0.2 (0.08)	0.1 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[0.06, 0.27]	[-0.03, 0.27]	[0.02, 0.33]	[-0.05, 0.35]	[0.07, 0.25]	[0.01, 0.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.02		0.02	
95% CI	[-0.14, 0.23]		[-0.23, 0.28]		[-0.13, 0.18]	
p-value	0.6553		0.8662		0.7670	
Hedges' g	0.15		-0.03		0.04	
95% CI	[-0.33, 0.63]		[-0.52, 0.45]		[-0.30, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.5.1.1.1.s4
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5381		0.6501		0.6809	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	61/85	26/48	52/98	28/46	113/183	54/94
Mean (SD)	53.2 (60.64)	51.8 (36.74)	35.4 (26.62)	30.5 (21.85)	45.0 (48.71)	40.8 (31.56)
Visit 13/ET						
n/N1	46/85	20/48	53/98	12/46	99/183	32/94
Mean (SD)	57.7 (55.98)	57.2 (64.41)	60.5 (68.66)	57.6 (70.48)	59.2 (62.79)	57.3 (65.62)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.3 (9.14)	5.5 (14.13)	32.9 (12.74)	23.9 (23.43)	19.5 (7.62)	13.4 (13.01)
95% CI	[-11.05, 25.56]	[-22.80, 33.79]	[7.21, 58.52]	[-23.26, 71.12]	[4.35, 34.55]	[-12.37, 39.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.76		8.93		6.03	
95% CI	[-31.94, 35.46]		[-44.89, 62.74]		[-23.85, 35.92]	
p-value	0.9171		0.7399		0.6897	
Hedges' g	0.03		0.06		0.07	
95% CI	[-0.52, 0.57]		[-0.60, 0.72]		[-0.36, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_5_1_1_1_m_fgf23_race.sas using SAS 9.4

Table 12.5.1.1.1.s4
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	36/56	15/24	32/46	19/26	68/102	34/50
Mean (SD)	37.0 (25.11)	32.5 (29.23)	34.1 (21.64)	43.5 (38.18)	35.7 (23.41)	38.6 (34.47)
Visit 13/ET						
n/N2	31/56	6/24	22/46	16/26	53/102	22/50
Mean (SD)	41.9 (36.71)	44.1 (35.89)	60.5 (69.13)	65.5 (44.41)	49.6 (52.84)	59.6 (42.55)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.5 (7.69)	6.3 (16.33)	26.5 (16.37)	22.6 (18.83)	17.1 (8.43)	14.5 (13.49)
95% CI	[-8.17, 23.27]	[-27.07, 39.74]	[-7.06, 60.10]	[-16.02, 61.25]	[0.21, 33.97]	[-12.56, 41.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.21		3.91		2.64	
95% CI	[-36.07, 38.50]		[-48.40, 56.22]		[-29.72, 35.00]	
p-value	0.9474		0.8793		0.8709	
Hedges' g	0.35		0.29		0.21	
95% CI	[-0.52, 1.22]		[-0.42, 0.99]		[-0.33, 0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_5_1_1_1_m_fgf23_race.sas using SAS 9.4

Table 12.4.12.1.2.s4
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0176		0.0052		0.0002	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	28.8 (9.92)	31.3 (11.09)	29.9 (9.28)	30.4 (8.63)	29.4 (9.57)	30.9 (9.92)
Visit 13/ET						
n/N1	78/85	45/48	90/98	40/46	168/183	85/94
Mean (SD)	27.2 (9.87)	31.8 (12.10)	27.6 (9.56)	30.3 (10.72)	27.4 (9.68)	31.1 (11.43)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.5 (0.69)	0.7 (0.91)	-2.4 (0.52)	-0.3 (0.78)	-1.9 (0.43)	0.2 (0.60)
95% CI	[-2.87, -0.14]	[-1.12, 2.47]	[-3.42, -1.37]	[-1.82, 1.26]	[-2.77, -1.09]	[-1.02, 1.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-2.18		-2.11		-2.10	
95% CI	[-4.45, 0.08]		[-3.96, -0.26]		[-3.55, -0.65]	
p-value	0.0590		0.0255		0.0048	
Hedges' g	-0.29		-0.42		-0.36	
95% CI	[-0.65, 0.08]		[-0.80, -0.05]		[-0.62, -0.09]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_2_m_egfr_race.sas using SAS 9.4

Table 12.4.12.1.2.s4
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	45/46	26/26	101/102	50/50
Mean (SD)	32.6 (12.35)	34.3 (10.84)	33.2 (11.00)	34.2 (10.87)	32.9 (11.71)	34.3 (10.74)
Visit 13/ET						
n/N2	53/56	23/24	42/46	22/26	95/102	45/50
Mean (SD)	33.7 (13.44)	32.3 (9.92)	33.4 (14.19)	30.5 (10.53)	33.6 (13.71)	31.4 (10.15)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	1.0 (1.12)	-2.3 (1.70)	0.8 (1.16)	-2.8 (1.61)	0.9 (0.81)	-2.6 (1.18)
95% CI	[-1.18, 3.28]	[-5.72, 1.06]	[-1.52, 3.13]	[-6.06, 0.36]	[-0.67, 2.55]	[-4.95, -0.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.38		3.65		3.56	
95% CI	[-0.69, 7.44]		[-0.32, 7.62]		[0.73, 6.40]	
p-value	0.1019		0.0705		0.0141	
Hedges' g	0.46		0.49		0.47	
95% CI	[-0.03, 0.95]		[-0.03, 1.00]		[0.12, 0.83]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_2_m_egfr_race.sas using SAS 9.4

Table 12.4.15.1.1.s4
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6556		0.3566		0.5550	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	68/85	43/48	75/98	34/46	143/183	77/94
Mean (SD)	0.6 (0.78)	0.6 (0.84)	0.8 (1.10)	0.8 (1.11)	0.7 (0.96)	0.7 (0.96)
Visit 13/ET						
n/N1	61/85	43/48	64/98	27/46	125/183	70/94
Mean (SD)	0.6 (1.05)	0.6 (0.84)	1.0 (1.45)	0.8 (1.14)	0.8 (1.28)	0.7 (0.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.10)	0.0 (0.11)	0.1 (0.10)	0.0 (0.16)	0.1 (0.07)	0.0 (0.10)
95% CI	[-0.19, 0.20]	[-0.22, 0.23]	[-0.07, 0.33]	[-0.30, 0.33]	[-0.07, 0.21]	[-0.18, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.00		0.11		0.06	
95% CI	[-0.29, 0.30]		[-0.26, 0.49]		[-0.18, 0.29]	
p-value	0.9920		0.5527		0.6456	
Hedges' g	-0.01		0.14		0.07	
95% CI	[-0.40, 0.38]		[-0.32, 0.59]		[-0.23, 0.36]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_15_1_1_m_ua_race.sas using SAS 9.4

Table 12.4.15.1.1.s4
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	48/56	19/24	35/46	21/26	83/102	40/50
Mean (SD)	0.6 (0.75)	0.7 (1.03)	0.7 (0.88)	1.0 (1.37)	0.6 (0.80)	0.9 (1.22)
Visit 13/ET						
n/N2	44/56	17/24	33/46	16/26	77/102	33/50
Mean (SD)	0.8 (1.17)	0.7 (0.95)	0.8 (1.01)	1.0 (2.28)	0.8 (1.09)	0.9 (1.71)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.10)	0.1 (0.17)	0.1 (0.22)	0.4 (0.31)	0.2 (0.11)	0.2 (0.17)
95% CI	[-0.05, 0.37]	[-0.29, 0.41]	[-0.30, 0.59]	[-0.21, 1.04]	[-0.07, 0.38]	[-0.10, 0.58]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.27		-0.08	
95% CI	[-0.30, 0.51]		[-1.04, 0.50]		[-0.49, 0.32]	
p-value	0.6193		0.4827		0.6825	
Hedges' g	0.14		-0.21		-0.09	
95% CI	[-0.42, 0.71]		[-0.81, 0.38]		[-0.50, 0.33]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_15_1_1_m_ua_race.sas using SAS 9.4

Table 12.4.12.1.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4965		0.0424		0.4343	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	9.3 (0.29)	9.3 (0.28)	9.3 (0.35)	9.3 (0.25)	9.3 (0.32)	9.3 (0.26)
Visit 13/ET						
n/N1	64/71	35/36	72/80	28/35	136/151	63/71
Mean (SD)	9.5 (0.45)	9.3 (0.29)	9.5 (0.38)	9.5 (0.50)	9.5 (0.42)	9.4 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.04)	0.2 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.17, 0.35]	[-0.05, 0.19]	[0.19, 0.34]	[0.11, 0.34]	[0.21, 0.32]	[0.06, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.04		0.12	
95% CI	[0.04, 0.34]		[-0.10, 0.18]		[0.02, 0.22]	
p-value	0.0114		0.5542		0.0199	
Hedges' g	0.58		0.14		0.40	
95% CI	[0.17, 1.00]		[-0.30, 0.57]		[0.10, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_1_m_dca_ckd.sas using SAS 9.4

Table 12.4.12.1.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	9.1 (0.27)	9.2 (0.28)	9.2 (0.35)	9.2 (0.31)	9.2 (0.31)	9.2 (0.29)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	9.5 (0.55)	9.3 (0.36)	9.5 (0.42)	9.2 (0.55)	9.5 (0.49)	9.3 (0.47)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.2 (0.07)	0.3 (0.05)	0.0 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.22, 0.43]	[0.02, 0.31]	[0.20, 0.41]	[-0.13, 0.14]	[0.24, 0.39]	[-0.01, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.16		0.30		0.23	
95% CI	[-0.02, 0.34]		[0.14, 0.47]		[0.11, 0.35]	
p-value	0.0797		0.0005		0.0002	
Hedges' g	0.38		0.77		0.57	
95% CI	[-0.04, 0.80]		[0.34, 1.20]		[0.27, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_1_m_dca_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4333		0.8830		0.4747	
Comparison Baseline vs. EAP	0.8289		0.4238		0.6219	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	3.5 (0.51)	3.7 (0.55)	3.6 (0.52)	3.6 (0.43)	3.5 (0.52)	3.6 (0.49)
Visit 13/ET						
n/N1	64/71	35/36	72/80	28/35	136/151	63/71
Mean (SD)	3.6 (0.58)	3.8 (0.61)	3.7 (0.60)	3.6 (0.68)	3.7 (0.59)	3.7 (0.65)
EAP						
n/N1	64/71	35/36	74/80	31/35	138/151	66/71
Mean (SD)	3.6 (0.49)	3.8 (0.54)	3.7 (0.48)	3.6 (0.46)	3.7 (0.48)	3.7 (0.51)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.1 (0.06)	-0.0 (0.09)	0.1 (0.04)	0.1 (0.06)
95% CI	[0.01, 0.26]	[-0.01, 0.33]	[0.01, 0.24]	[-0.21, 0.16]	[0.05, 0.22]	[-0.06, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.15		0.07	
95% CI	[-0.24, 0.18]		[-0.07, 0.37]		[-0.08, 0.22]	
p-value	0.8074		0.1750		0.3703	
Hedges' g	0.10		0.30		0.18	
95% CI	[-0.31, 0.51]		[-0.14, 0.73]		[-0.12, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.1 (0.04)	0.0 (0.06)	0.1 (0.03)	0.1 (0.04)
95% CI	[0.05, 0.24]	[0.01, 0.27]	[0.03, 0.18]	[-0.07, 0.17]	[0.07, 0.19]	[0.00, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.06		0.04	
95% CI	[-0.16, 0.17]		[-0.08, 0.20]		[-0.07, 0.14]	
p-value	0.9234		0.3879		0.5042	
Hedges' g	0.19		0.16		0.17	
95% CI	[-0.22, 0.60]		[-0.25, 0.58]		[-0.12, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	3.9 (0.48)	4.0 (0.59)	4.0 (0.54)	3.8 (0.49)	4.0 (0.51)	3.9 (0.55)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	4.2 (0.72)	4.0 (0.71)	4.4 (0.74)	3.9 (0.71)	4.3 (0.73)	3.9 (0.71)
EAP						
n/N2	67/70	34/36	62/64	34/37	129/134	68/73
Mean (SD)	4.1 (0.65)	4.1 (0.57)	4.4 (0.72)	3.9 (0.57)	4.2 (0.69)	4.0 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.0 (0.11)	0.4 (0.09)	0.0 (0.12)	0.3 (0.06)	0.0 (0.08)
95% CI	[0.08, 0.39]	[-0.20, 0.24]	[0.23, 0.58]	[-0.19, 0.28]	[0.20, 0.43]	[-0.12, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.22		0.37		0.28	
95% CI	[-0.05, 0.48]		[0.07, 0.66]		[0.09, 0.48]	
p-value	0.1123		0.0165		0.0049	
Hedges' g	0.33		0.34		0.33	
95% CI	[-0.08, 0.75]		[-0.08, 0.76]		[0.04, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.4 (0.07)	0.1 (0.10)	0.3 (0.05)	0.1 (0.06)
95% CI	[0.07, 0.29]	[-0.03, 0.28]	[0.25, 0.55]	[-0.14, 0.27]	[0.19, 0.38]	[-0.02, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.33		0.18	
95% CI	[-0.14, 0.25]		[0.08, 0.59]		[0.03, 0.34]	
p-value	0.5907		0.0101		0.0216	
Hedges' g	0.13		0.40		0.27	
95% CI	[-0.28, 0.54]		[-0.02, 0.82]		[-0.02, 0.57]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.5.1.1.1.s5
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8531		0.1794		0.2804	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	40/71	15/36	41/80	21/35	81/151	36/71
Mean (SD)	41.6 (30.73)	47.2 (43.29)	35.7 (28.92)	29.1 (18.41)	38.6 (29.78)	36.6 (32.02)
Visit 13/ET						
n/N1	30/71	11/36	32/80	10/35	62/151	21/71
Mean (SD)	31.6 (22.58)	42.2 (32.99)	38.5 (27.83)	57.5 (46.40)	35.2 (25.45)	49.5 (39.67)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-8.9 (5.23)	-3.1 (8.39)	2.3 (8.37)	13.5 (13.25)	-3.8 (4.89)	6.3 (7.77)
95% CI	[-19.56, 1.82]	[-20.23, 14.08]	[-14.96, 19.51]	[-13.77, 40.80]	[-13.61, 5.98]	[-9.28, 21.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-5.80		-11.24		-10.10	
95% CI	[-26.08, 14.48]		[-43.54, 21.07]		[-28.50, 8.30]	
p-value	0.5633		0.4804		0.2761	
Hedges' g	0.01		-0.31		-0.18	
95% CI	[-0.74, 0.76]		[-1.11, 0.49]		[-0.73, 0.38]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_5_1_1_1_m_fgf23_ckd.sas using SAS 9.4

Table 12.5.1.1.1.s5
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	57/70	26/36	43/64	26/37	100/134	52/73
Mean (SD)	51.2 (61.18)	43.4 (30.25)	34.1 (20.22)	41.1 (36.11)	43.9 (48.61)	42.2 (33.00)
Visit 13/ET						
n/N2	47/70	15/36	43/64	18/37	90/134	33/73
Mean (SD)	63.9 (57.51)	62.9 (71.95)	76.8 (83.75)	64.7 (61.81)	70.1 (71.14)	63.9 (65.54)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	15.0 (9.10)	12.5 (15.95)	49.8 (14.18)	23.6 (20.83)	31.2 (8.14)	19.3 (12.94)
95% CI	[-3.23, 33.22]	[-19.47, 44.38]	[21.25, 78.29]	[-18.26, 65.53]	[15.02, 47.29]	[-6.35, 44.95]
Diff in LS-Mean [ER-Calcifediol - Placebo]	2.54		26.13		11.85	
95% CI	[-34.24, 39.32]		[-25.02, 77.29]		[-18.51, 42.21]	
p-value	0.8906		0.3093		0.4407	
Hedges' g	0.10		0.37		0.20	
95% CI	[-0.48, 0.67]		[-0.22, 0.96]		[-0.21, 0.61]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_5_1_1_1_m_fgf23_ckd.sas using SAS 9.4

Table 12.4.12.1.2.s5
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5312		0.8602		0.5998	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	38.4 (9.19)	40.3 (9.41)	37.4 (7.97)	39.0 (7.52)	37.9 (8.55)	39.6 (8.49)
Visit 13/ET						
n/N1	64/71	35/36	72/80	28/35	136/151	63/71
Mean (SD)	38.0 (9.55)	38.9 (9.54)	36.6 (10.34)	38.5 (8.25)	37.3 (9.97)	38.7 (8.92)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.90)	-0.8 (1.21)	-0.9 (0.84)	-0.4 (1.35)	-0.7 (0.62)	-0.6 (0.91)
95% CI	[-2.25, 1.31]	[-3.26, 1.56]	[-2.52, 0.80]	[-3.11, 2.24]	[-1.88, 0.55]	[-2.42, 1.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.38		-0.42		-0.04	
95% CI	[-2.62, 3.38]		[-3.57, 2.73]		[-2.21, 2.13]	
p-value	0.8040		0.7908		0.9700	
Hedges' g	0.12		-0.03		0.05	
95% CI	[-0.29, 0.53]		[-0.46, 0.41]		[-0.24, 0.35]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_2_m_egfr_ckd.sas using SAS 9.4

Table 12.4.12.1.2.s5
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	63/64	37/37	133/134	73/73
Mean (SD)	22.2 (5.32)	24.4 (5.38)	22.7 (4.73)	24.9 (5.50)	22.4 (5.04)	24.7 (5.41)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	22.0 (7.86)	24.7 (8.15)	20.9 (5.27)	23.7 (7.00)	21.4 (6.76)	24.2 (7.55)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.81)	0.3 (1.17)	-2.2 (0.57)	-1.4 (0.77)	-1.4 (0.51)	-0.5 (0.70)
95% CI	[-2.14, 1.10]	[-2.02, 2.62]	[-3.38, -1.10]	[-2.92, 0.13]	[-2.38, -0.38]	[-1.93, 0.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.82		-0.85		-0.83	
95% CI	[-3.67, 2.03]		[-2.78, 1.08]		[-2.55, 0.89]	
p-value	0.5698		0.3833		0.3421	
Hedges' g	-0.06		-0.08		-0.06	
95% CI	[-0.48, 0.35]		[-0.50, 0.34]		[-0.35, 0.24]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_2_m_egfr_ckd.sas using SAS 9.4

Table 12.4.15.1.1.s5
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6638		0.3660		0.7469	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	54/71	28/36	55/80	21/35	109/151	49/71
Mean (SD)	0.4 (0.61)	0.4 (0.85)	0.6 (0.86)	0.8 (1.36)	0.5 (0.75)	0.6 (1.10)
Visit 13/ET						
n/N1	46/71	29/36	49/80	19/35	95/151	48/71
Mean (SD)	0.6 (1.08)	0.5 (0.96)	0.6 (0.95)	0.9 (1.25)	0.6 (1.01)	0.6 (1.09)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.10)	0.1 (0.13)	0.1 (0.11)	0.3 (0.18)	0.1 (0.08)	0.2 (0.11)
95% CI	[-0.04, 0.37]	[-0.20, 0.33]	[-0.13, 0.33]	[-0.06, 0.66]	[-0.02, 0.29]	[-0.04, 0.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.20		-0.05	
95% CI	[-0.24, 0.44]		[-0.63, 0.23]		[-0.31, 0.22]	
p-value	0.5540		0.3497		0.7310	
Hedges' g	0.15		-0.25		-0.03	
95% CI	[-0.32, 0.61]		[-0.79, 0.29]		[-0.38, 0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_15_1_1_m_ua_ckd.sas using SAS 9.4

Table 12.4.15.1.1.s5
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	62/70	34/36	55/64	34/37	117/134	68/73
Mean (SD)	0.8 (0.84)	0.9 (0.90)	1.0 (1.16)	0.9 (1.12)	0.9 (1.00)	0.9 (1.01)
Visit 13/ET						
n/N2	59/70	31/36	48/64	24/37	107/134	55/73
Mean (SD)	0.8 (1.11)	0.8 (0.75)	1.2 (1.57)	0.9 (1.91)	1.0 (1.34)	0.9 (1.37)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.10)	-0.0 (0.13)	0.2 (0.16)	0.1 (0.23)	0.1 (0.09)	0.0 (0.13)
95% CI	[-0.20, 0.19]	[-0.28, 0.26]	[-0.16, 0.49]	[-0.39, 0.54]	[-0.10, 0.26]	[-0.23, 0.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.00		0.09		0.05	
95% CI	[-0.33, 0.33]		[-0.48, 0.65]		[-0.26, 0.37]	
p-value	0.9905		0.7610		0.7351	
Hedges' g	0.01		0.08		0.05	
95% CI	[-0.43, 0.44]		[-0.40, 0.57]		[-0.27, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_15_1_1_m_ua_ckd.sas using SAS 9.4

Table 12.4.12.1.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7403		0.7190		0.5798	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	9.3 (0.27)	9.2 (0.28)	9.3 (0.29)	9.3 (0.30)	9.3 (0.28)	9.3 (0.29)
Visit 13/ET						
n/N1	40/43	25/26	49/53	18/20	89/96	43/46
Mean (SD)	9.5 (0.48)	9.3 (0.34)	9.6 (0.33)	9.4 (0.63)	9.6 (0.41)	9.4 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.07)	0.3 (0.04)	0.2 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.10, 0.33]	[-0.06, 0.23]	[0.20, 0.38]	[0.03, 0.32]	[0.18, 0.33]	[0.03, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.12		0.13	
95% CI	[-0.05, 0.31]		[-0.06, 0.29]		[0.00, 0.25]	
p-value	0.1548		0.1789		0.0479	
Hedges' g	0.36		0.38		0.40	
95% CI	[-0.14, 0.86]		[-0.16, 0.92]		[0.04, 0.77]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_1_m_dca_ttlpth.sas using SAS 9.4

Table 12.4.12.1.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	9.2 (0.27)	9.2 (0.30)	9.3 (0.39)	9.3 (0.22)	9.2 (0.33)	9.3 (0.26)
Visit 13/ET						
n/N2	47/50	22/22	43/44	23/28	90/94	45/50
Mean (SD)	9.4 (0.41)	9.3 (0.31)	9.5 (0.39)	9.4 (0.40)	9.4 (0.41)	9.3 (0.36)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.1 (0.07)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.10, 0.29]	[-0.07, 0.22]	[0.12, 0.33]	[-0.07, 0.21]	[0.14, 0.28]	[-0.03, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.15		0.14	
95% CI	[-0.05, 0.30]		[-0.02, 0.33]		[0.01, 0.26]	
p-value	0.1568		0.0890		0.0293	
Hedges' g	0.42		0.41		0.42	
95% CI	[-0.08, 0.93]		[-0.10, 0.91]		[0.06, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_1_m_dca_ttlpth.sas using SAS 9.4

Table 12.4.12.1.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	9.1 (0.31)	9.2 (0.28)	9.1 (0.33)	9.2 (0.33)	9.1 (0.32)	9.2 (0.30)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	9.6 (0.59)	9.4 (0.31)	9.4 (0.45)	9.3 (0.61)	9.5 (0.53)	9.3 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.5 (0.07)	0.2 (0.10)	0.3 (0.06)	0.1 (0.09)	0.4 (0.05)	0.1 (0.07)
95% CI	[0.33, 0.61]		[0.21, 0.47]		[0.31, 0.50]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.28		0.28		0.28	
95% CI	[0.04, 0.52]		[0.07, 0.50]		[0.12, 0.44]	
p-value	0.0237		0.0114		0.0008	
Hedges' g	0.63		0.66		0.65	
95% CI	[0.11, 1.16]		[0.13, 1.20]		[0.28, 1.03]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_1_m_dca_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6889		0.5841		0.9897	
Comparison Baseline vs. EAP	0.2062		0.4883		0.9254	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	3.5 (0.50)	3.7 (0.53)	3.6 (0.52)	3.5 (0.49)	3.6 (0.51)	3.6 (0.51)
Visit 13/ET						
n/N1	40/43	25/26	49/53	18/20	89/96	43/46
Mean (SD)	3.7 (0.55)	3.8 (0.68)	3.9 (0.65)	3.5 (0.48)	3.8 (0.61)	3.7 (0.61)
EAP						
n/N1	40/43	25/26	52/53	18/20	92/96	43/46
Mean (SD)	3.7 (0.52)	3.8 (0.56)	3.9 (0.59)	3.6 (0.41)	3.8 (0.57)	3.7 (0.51)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.2 (0.11)	0.2 (0.07)	-0.0 (0.11)	0.2 (0.05)	0.1 (0.08)
95% CI	[-0.01, 0.33]	[-0.05, 0.38]	[0.11, 0.38]	[-0.24, 0.20]	[0.10, 0.32]	[-0.09, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.27		0.14	
95% CI	[-0.28, 0.27]		[0.00, 0.53]		[-0.04, 0.33]	
p-value	0.9696		0.0460		0.1338	
Hedges' g	0.09		0.47		0.26	
95% CI	[-0.40, 0.59]		[-0.07, 1.01]		[-0.11, 0.62]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.2 (0.05)	0.1 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.01, 0.26]	[0.04, 0.35]	[0.15, 0.35]	[-0.09, 0.25]	[0.12, 0.27]	[0.02, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.05		0.17		0.06	
95% CI	[-0.26, 0.15]		[-0.03, 0.36]		[-0.07, 0.20]	
p-value	0.5931		0.0946		0.3635	
Hedges' g	-0.03		0.40		0.17	
95% CI	[-0.53, 0.46]		[-0.14, 0.93]		[-0.19, 0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	3.7 (0.57)	3.9 (0.51)	3.7 (0.59)	3.7 (0.42)	3.7 (0.57)	3.8 (0.46)
Visit 13/ET						
n/N2	47/50	22/22	43/44	23/28	90/94	45/50
Mean (SD)	4.0 (0.70)	3.9 (0.67)	3.9 (0.71)	3.9 (0.90)	4.0 (0.70)	3.9 (0.79)
EAP						
n/N2	47/50	22/22	43/44	24/28	90/94	46/50
Mean (SD)	4.0 (0.55)	3.9 (0.56)	3.9 (0.58)	3.9 (0.63)	3.9 (0.56)	3.9 (0.59)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.0 (0.12)	0.2 (0.10)	0.2 (0.13)	0.2 (0.06)	0.1 (0.09)
95% CI	[0.05, 0.38]	[-0.22, 0.26]	[0.02, 0.40]	[-0.11, 0.41]	[0.09, 0.34]	[-0.09, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.06		0.13	
95% CI	[-0.10, 0.49]		[-0.26, 0.38]		[-0.08, 0.35]	
p-value	0.1871		0.7150		0.2253	
Hedges' g	0.40		0.10		0.24	
95% CI	[-0.10, 0.91]		[-0.41, 0.60]		[-0.11, 0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.1 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.13, 0.35]	[-0.11, 0.22]	[0.00, 0.27]	[-0.05, 0.31]	[0.10, 0.27]	[-0.03, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.01		0.10	
95% CI	[-0.01, 0.38]		[-0.21, 0.24]		[-0.05, 0.25]	
p-value	0.0642		0.9229		0.1876	
Hedges' g	0.55		0.02		0.27	
95% CI	[0.04, 1.06]		[-0.48, 0.51]		[-0.09, 0.62]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	3.9 (0.53)	4.0 (0.68)	4.0 (0.55)	3.8 (0.48)	3.9 (0.54)	3.9 (0.59)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	4.1 (0.80)	4.0 (0.65)	4.2 (0.83)	3.7 (0.62)	4.1 (0.82)	3.9 (0.64)
EAP						
n/N3	44/48	22/24	41/47	23/24	85/95	45/48
Mean (SD)	4.0 (0.74)	4.1 (0.62)	4.3 (0.80)	3.8 (0.48)	4.1 (0.78)	3.9 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.1 (0.14)	0.3 (0.12)	-0.1 (0.16)	0.2 (0.07)	-0.0 (0.10)
95% CI	[-0.01, 0.36]		[0.06, 0.52]		[0.08, 0.37]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.39		0.23	
95% CI	[-0.22, 0.44]		[-0.01, 0.79]		[-0.02, 0.48]	
p-value	0.5206		0.0560		0.0747	
Hedges' g	0.19		0.35		0.28	
95% CI	[-0.32, 0.71]		[-0.17, 0.88]		[-0.09, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.11)	0.3 (0.10)	-0.0 (0.14)	0.2 (0.06)	0.1 (0.09)
95% CI	[-0.05, 0.26]		[0.14, 0.54]		[0.09, 0.34]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.37		0.16	
95% CI	[-0.28, 0.26]		[0.03, 0.72]		[-0.05, 0.37]	
p-value	0.9259		0.0327		0.1368	
Hedges' g	0.01		0.39		0.22	
95% CI	[-0.49, 0.52]		[-0.11, 0.90]		[-0.14, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.5.1.1.1.s6
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7318		0.8697		0.9921	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	19/43	10/26	24/53	8/20	43/96	18/46
Mean (SD)	41.2 (34.97)	43.5 (38.63)	36.1 (31.75)	26.7 (16.37)	38.4 (32.90)	36.0 (31.22)
Visit 13/ET						
n/N1	15/43	6/26	25/53	5/20	40/96	11/46
Mean (SD)	35.8 (27.20)	46.6 (28.85)	40.9 (27.16)	31.6 (22.50)	39.0 (26.94)	39.8 (26.08)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-5.1 (6.49)	-2.9 (10.47)	10.1 (6.65)	-8.1 (10.78)	1.8 (5.11)	-3.8 (8.24)
95% CI	[-18.97, 8.69]	[-25.21, 19.43]	[-4.12, 24.24]	[-31.03, 14.93]	[-8.62, 12.22]	[-20.58, 13.05]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-2.25		18.11		5.57	
95% CI	[-28.52, 24.02]		[-9.01, 45.24]		[-14.22, 25.36]	
p-value	0.8574		0.1751		0.5702	
Hedges' g	-0.03		0.11		0.06	
95% CI	[-1.01, 0.95]		[-0.88, 1.09]		[-0.66, 0.77]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_5_1_1_1_m_fgf23_ttlpth.sas using SAS 9.4

Table 12.5.1.1.1.s6
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	38/50	13/22	26/44	18/28	64/94	31/50
Mean (SD)	36.4 (19.45)	31.7 (34.34)	37.1 (25.02)	25.8 (17.09)	36.6 (21.70)	28.3 (25.42)
Visit 13/ET						
n/N2	28/50	7/22	26/44	9/28	54/94	16/50
Mean (SD)	46.0 (46.97)	40.3 (42.87)	71.1 (79.63)	69.4 (50.06)	58.1 (65.38)	56.7 (47.89)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	13.4 (9.35)	-1.4 (18.94)	46.7 (19.58)	39.4 (35.16)	29.4 (10.11)	21.0 (19.02)
95% CI	[-5.76, 32.60]	[-40.30, 37.43]	[6.05, 87.28]	[-33.55, 112.29]	[9.09, 49.72]	[-17.17, 59.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	14.86		7.30		8.37	
95% CI	[-28.78, 58.49]		[-76.69, 91.28]		[-34.91, 51.65]	
p-value	0.4907		0.8587		0.6993	
Hedges' g	0.41		-0.01		0.11	
95% CI	[-0.47, 1.29]		[-0.90, 0.88]		[-0.52, 0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_5_1_1_1_m_fgf23_ttlpth.sas using SAS 9.4

Table 12.5.1.1.1.s6
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	40/48	18/24	34/47	21/24	74/95	39/48
Mean (SD)	60.4 (71.70)	54.9 (32.20)	32.4 (18.65)	47.7 (37.91)	47.5 (55.69)	51.0 (35.12)
Visit 13/ET						
n/N3	34/48	13/24	24/47	14/24	58/95	27/48
Mean (SD)	62.6 (57.05)	65.1 (75.08)	69.3 (82.05)	68.3 (66.16)	65.4 (67.91)	66.8 (69.23)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.9 (11.36)	9.9 (17.82)	33.8 (17.22)	20.5 (22.80)	18.7 (9.87)	17.7 (13.98)
95% CI	[-14.03, 31.80]		[-1.30, 68.88]		[-0.95, 38.39]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.98		13.24		0.98	
95% CI	[-43.62, 41.66]		[-46.77, 73.25]		[-33.22, 35.18]	
p-value	0.9633		0.6561		0.9547	
Hedges' g	0.01		0.28		0.11	
95% CI	[-0.62, 0.64]		[-0.39, 0.96]		[-0.35, 0.57]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_5_1_1_1_m_fgf23_ttlpth.sas using SAS 9.4

Table 12.4.12.1.2.s6
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7811		0.7099		0.9030	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	37.4 (12.72)	38.9 (11.92)	34.0 (10.63)	37.4 (8.67)	35.5 (11.67)	38.2 (10.55)
Visit 13/ET						
n/N1	40/43	25/26	49/53	18/20	89/96	43/46
Mean (SD)	36.2 (12.33)	37.7 (11.77)	33.3 (12.76)	35.5 (10.10)	34.6 (12.58)	36.8 (11.03)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.1 (1.15)	-0.7 (1.46)	-0.6 (0.99)	-1.4 (1.64)	-0.9 (0.77)	-0.9 (1.11)
95% CI	[-3.45, 1.16]	[-3.65, 2.19]	[-2.56, 1.40]	[-4.65, 1.92]	[-2.40, 0.63]	[-3.15, 1.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.42		0.79		0.06	
95% CI	[-4.14, 3.31]		[-3.06, 4.63]		[-2.62, 2.74]	
p-value	0.8244		0.6848		0.9659	
Hedges' g	-0.01		0.12		0.05	
95% CI	[-0.51, 0.48]		[-0.42, 0.65]		[-0.32, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_2_m_egfr_ttlpth.sas using SAS 9.4

Table 12.4.12.1.2.s6
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	29.1 (8.38)	30.8 (8.60)	31.2 (8.87)	32.4 (9.48)	30.1 (8.62)	31.7 (9.05)
Visit 13/ET						
n/N2	47/50	22/22	43/44	23/28	90/94	45/50
Mean (SD)	28.6 (9.91)	31.1 (10.53)	29.2 (10.60)	31.6 (11.30)	28.9 (10.19)	31.3 (10.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.2 (0.93)	0.4 (1.36)	-1.7 (0.90)	-1.3 (1.23)	-1.0 (0.65)	-0.5 (0.91)
95% CI	[-2.08, 1.62]	[-2.35, 3.07]	[-3.50, 0.10]	[-3.77, 1.16]	[-2.24, 0.31]	[-2.28, 1.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.59		-0.40		-0.49	
95% CI	[-3.88, 2.70]		[-3.46, 2.66]		[-2.71, 1.73]	
p-value	0.7197		0.7959		0.6623	
Hedges' g	-0.07		-0.07		-0.06	
95% CI	[-0.57, 0.43]		[-0.57, 0.43]		[-0.42, 0.29]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_2_m_egfr_ttlpth.sas using SAS 9.4

Table 12.4.12.1.2.s6
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	46/47	24/24	94/95	48/48
Mean (SD)	25.3 (8.60)	26.6 (8.26)	27.2 (8.94)	26.3 (7.64)	26.2 (8.78)	26.5 (7.87)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	25.3 (11.01)	26.2 (8.44)	25.0 (9.21)	24.6 (7.32)	25.1 (10.13)	25.4 (7.85)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (1.14)	-0.9 (1.66)	-1.9 (0.82)	-1.1 (1.13)	-0.9 (0.71)	-1.0 (1.00)
95% CI	[-2.25, 2.32]		[-3.56, -0.29]		[-2.34, 0.46]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.97		-0.84		0.08	
95% CI	[-3.07, 5.01]		[-3.63, 1.95]		[-2.34, 2.51]	
p-value	0.6327		0.5503		0.9456	
Hedges' g	0.17		-0.20		0.03	
95% CI	[-0.34, 0.69]		[-0.72, 0.33]		[-0.34, 0.40]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_2_m_egfr_ttlpth.sas using SAS 9.4

Table 12.4.15.1.1.s6
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3105		0.8220		0.3759	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	32/43	21/26	35/53	12/20	67/96	33/46
Mean (SD)	0.7 (0.90)	0.5 (0.68)	0.5 (0.64)	0.7 (0.84)	0.6 (0.77)	0.5 (0.74)
Visit 13/ET						
n/N1	29/43	22/26	32/53	12/20	61/96	34/46
Mean (SD)	0.9 (1.31)	0.6 (0.98)	0.8 (1.10)	1.0 (1.52)	0.8 (1.20)	0.7 (1.19)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.12)	0.2 (0.14)	0.3 (0.17)	0.4 (0.27)	0.2 (0.10)	0.3 (0.14)
95% CI	[-0.13, 0.35]	[-0.12, 0.45]	[-0.07, 0.61]	[-0.15, 0.96]	[-0.01, 0.39]	[0.00, 0.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.05		-0.14		-0.10	
95% CI	[-0.43, 0.32]		[-0.79, 0.51]		[-0.44, 0.25]	
p-value	0.7845		0.6666		0.5851	
Hedges' g	0.00		-0.17		-0.04	
95% CI	[-0.55, 0.56]		[-0.85, 0.51]		[-0.47, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_15_1_1_m_ua_ttlpth.sas using SAS 9.4

Table 12.4.15.1.1.s6
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	40/50	19/22	36/44	21/28	76/94	40/50
Mean (SD)	0.5 (0.64)	0.9 (1.32)	0.8 (1.08)	0.4 (0.72)	0.7 (0.88)	0.7 (1.07)
Visit 13/ET						
n/N2	41/50	20/22	35/44	16/28	76/94	36/50
Mean (SD)	0.6 (1.10)	0.7 (0.88)	0.9 (1.11)	0.5 (0.79)	0.8 (1.10)	0.6 (0.83)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.13)	-0.1 (0.18)	0.1 (0.12)	-0.1 (0.18)	0.1 (0.09)	-0.1 (0.13)
95% CI	[-0.17, 0.34]	[-0.48, 0.24]	[-0.13, 0.36]	[-0.42, 0.30]	[-0.07, 0.27]	[-0.34, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.17		0.19	
95% CI	[-0.24, 0.65]		[-0.26, 0.61]		[-0.12, 0.49]	
p-value	0.3619		0.4325		0.2230	
Hedges' g	0.36		0.11		0.25	
95% CI	[-0.18, 0.89]		[-0.48, 0.69]		[-0.14, 0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_15_1_1_m_ua_ttlpth.sas using SAS 9.4

Table 12.4.15.1.1.s6
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	44/48	22/24	39/47	22/24	83/95	44/48
Mean (SD)	0.7 (0.78)	0.6 (0.54)	0.9 (1.25)	1.4 (1.52)	0.8 (1.03)	1.0 (1.20)
Visit 13/ET						
n/N3	35/48	18/24	30/47	15/24	65/95	33/48
Mean (SD)	0.7 (0.91)	0.6 (0.75)	1.0 (1.72)	1.2 (2.28)	0.8 (1.35)	0.9 (1.64)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.12)	0.1 (0.16)	0.1 (0.23)	0.1 (0.32)	0.0 (0.12)	0.1 (0.17)
95% CI	[-0.26, 0.21]		[-0.39, 0.53]		[-0.23, 0.25]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.12		-0.08		-0.13	
95% CI	[-0.52, 0.28]		[-0.87, 0.72]		[-0.55, 0.29]	
p-value	0.5517		0.8467		0.5323	
Hedges' g	-0.24		-0.07		-0.14	
95% CI	[-0.81, 0.32]		[-0.68, 0.54]		[-0.55, 0.28]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_15_1_1_m_ua_ttlpth.sas using SAS 9.4

Table 12.4.12.1.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3820		0.8430		0.4020	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	9.3 (0.31)	9.4 (0.36)	9.5 (0.39)	9.6 (0.17)	9.4 (0.38)	9.5 (0.28)
Visit 13/ET						
n/N1	17/18	5/5	29/32	4/5	46/50	9/10
Mean (SD)	9.7 (0.48)	9.5 (0.32)	9.8 (0.35)	9.8 (0.37)	9.8 (0.40)	9.6 (0.36)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.09)	0.1 (0.17)	0.4 (0.06)	0.2 (0.15)	0.4 (0.05)	0.1 (0.11)
95% CI	[0.20, 0.58]	[-0.27, 0.43]	[0.24, 0.47]	[-0.10, 0.51]	[0.26, 0.46]	[-0.08, 0.36]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.31		0.15		0.22	
95% CI	[-0.08, 0.70]		[-0.17, 0.48]		[-0.02, 0.47]	
p-value	0.1159		0.3511		0.0704	
Hedges' g	0.87		0.58		0.76	
95% CI	[-0.13, 1.86]		[-0.45, 1.61]		[0.04, 1.48]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_1_m_dca_dose.sas using SAS 9.4

Table 12.4.12.1.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	9.2 (0.27)	9.2 (0.27)	9.2 (0.29)	9.2 (0.26)	9.2 (0.28)	9.2 (0.26)
Visit 13/ET						
n/N2	106/108	62/63	95/98	56/61	201/206	118/124
Mean (SD)	9.4 (0.40)	9.3 (0.32)	9.5 (0.36)	9.3 (0.55)	9.4 (0.38)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.03)	0.1 (0.04)	0.3 (0.04)	0.1 (0.05)	0.3 (0.03)	0.1 (0.03)
95% CI	[0.18, 0.31]	[0.04, 0.21]	[0.19, 0.34]	[0.00, 0.20]	[0.21, 0.31]	[0.05, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.17		0.15	
95% CI	[0.02, 0.23]		[0.05, 0.29]		[0.07, 0.23]	
p-value	0.0237		0.0074		0.0004	
Hedges' g	0.40		0.47		0.44	
95% CI	[0.09, 0.72]		[0.14, 0.80]		[0.21, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_1_m_dca_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6373		0.5502		0.7414	
Comparison Baseline vs. EAP	0.4386		0.5553		0.6073	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	3.4 (0.59)	3.2 (0.50)	3.7 (0.37)	3.7 (0.51)	3.6 (0.49)	3.4 (0.54)
Visit 13/ET						
n/N1	17/18	5/5	29/32	4/5	46/50	9/10
Mean (SD)	3.8 (0.59)	3.7 (0.76)	3.9 (0.59)	3.5 (0.67)	3.9 (0.58)	3.6 (0.68)
EAP						
n/N1	17/18	5/5	31/32	5/5	48/50	10/10
Mean (SD)	3.7 (0.53)	3.6 (0.40)	3.9 (0.48)	3.7 (0.48)	3.8 (0.50)	3.6 (0.42)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.5 (0.14)	0.4 (0.25)	0.2 (0.09)	-0.2 (0.25)	0.3 (0.08)	0.1 (0.18)
95% CI	[0.18, 0.76]	[-0.13, 0.94]	[-0.03, 0.35]	[-0.69, 0.33]	[0.14, 0.46]	[-0.25, 0.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.07		0.34		0.20	
95% CI	[-0.54, 0.67]		[-0.20, 0.89]		[-0.19, 0.59]	
p-value	0.8234		0.2101		0.3168	
Hedges' g	-0.04		0.65		0.14	
95% CI	[-0.99, 0.92]		[-0.38, 1.68]		[-0.57, 0.84]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.3 (0.10)	0.4 (0.18)	0.2 (0.06)	-0.0 (0.14)	0.2 (0.05)	0.2 (0.12)
95% CI	[0.11, 0.53]	[-0.02, 0.74]	[0.05, 0.29]	[-0.32, 0.26]	[0.12, 0.34]	[-0.07, 0.39]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.20		0.07	
95% CI	[-0.48, 0.40]		[-0.11, 0.52]		[-0.19, 0.32]	
p-value	0.8504		0.2045		0.5868	
Hedges' g	-0.25		0.61		0.05	
95% CI	[-1.21, 0.71]		[-0.33, 1.54]		[-0.62, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	3.8 (0.53)	3.9 (0.58)	3.8 (0.61)	3.7 (0.45)	3.8 (0.57)	3.8 (0.53)
Visit 13/ET						
n/N2	106/108	62/63	95/98	56/61	201/206	118/124
Mean (SD)	3.9 (0.73)	3.9 (0.66)	4.1 (0.78)	3.7 (0.71)	4.0 (0.76)	3.8 (0.69)
EAP						
n/N2	106/108	63/63	97/98	58/61	203/206	121/124
Mean (SD)	3.9 (0.64)	4.0 (0.59)	4.1 (0.73)	3.7 (0.53)	4.0 (0.68)	3.9 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.07)	0.3 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.26]	[-0.09, 0.20]	[0.17, 0.43]	[-0.11, 0.22]	[0.14, 0.31]	[-0.05, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.24		0.17	
95% CI	[-0.08, 0.28]		[0.03, 0.46]		[0.03, 0.31]	
p-value	0.2918		0.0245		0.0156	
Hedges' g	0.21		0.32		0.26	
95% CI	[-0.11, 0.52]		[-0.01, 0.65]		[0.04, 0.49]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.04)	0.1 (0.05)	0.3 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.07, 0.23]	[-0.00, 0.21]	[0.18, 0.39]	[-0.05, 0.22]	[0.15, 0.28]	[0.01, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.20		0.12	
95% CI	[-0.09, 0.18]		[0.03, 0.37]		[0.01, 0.22]	
p-value	0.4984		0.0203		0.0272	
Hedges' g	0.15		0.31		0.23	
95% CI	[-0.16, 0.46]		[-0.02, 0.63]		[0.01, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.5.1.1.1.s7
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	NA		NA		0.9862	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	12/18	2/5	14/32	3/5	26/50	5/10
Mean (SD)	35.9 (22.88)	82.8 (85.91)	41.9 (30.88)	21.1 (6.30)	39.1 (27.12)	45.8 (54.81)
Visit 13/ET						
n/N1	9/18	1/5	12/32	1/5	21/50	2/10
Mean (SD)	26.2 (13.29)	18.2 (NA)	54.3 (74.61)	15.4 (NA)	42.2 (57.76)	16.8 (1.98)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-8.8 (4.72)	-17.7 (14.41)	15.9 (29.22)	-17.9 (90.74)	3.5 (14.42)	-17.8 (44.41)
95% CI	[-19.99, 2.34]	[-51.73, 16.40]	[-53.20, 84.99]	[-232.50, 196.61]	[-27.21, 34.28]	[-112.46, 76.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	8.84		33.84		21.34	
95% CI	[-27.14, 44.82]		[-193.26, 260.94]		[-78.74, 121.43]	
p-value	0.5795		0.7349		0.6559	
Hedges' g	NA		NA		0.11	
95% CI	NA		NA		[-1.29, 1.51]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_5_1_1_1_m_fgf23_dose.sas using SAS 9.4

Table 12.5.1.1.1.s7
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	75/108	38/63	61/98	42/61	136/206	80/124
Mean (SD)	48.2 (55.02)	42.8 (32.40)	34.2 (24.11)	32.9 (25.32)	41.9 (44.35)	37.6 (29.14)
Visit 13/ET						
n/N2	64/108	25/63	59/98	25/61	123/206	50/124
Mean (SD)	51.6 (49.37)	55.6 (59.41)	64.0 (69.23)	63.3 (58.33)	57.6 (59.80)	59.4 (58.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	6.6 (7.26)	7.0 (11.34)	38.4 (11.36)	28.6 (16.07)	21.8 (6.47)	17.3 (9.57)
95% CI	[-7.87, 21.06]	[-15.55, 29.62]	[15.67, 61.10]	[-3.52, 60.77]	[9.04, 34.63]	[-1.60, 36.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.44		9.76		4.52	
95% CI	[-27.28, 26.40]		[-29.63, 49.15]		[-18.33, 27.37]	
p-value	0.9742		0.6220		0.6963	
Hedges' g	0.08		0.16		0.10	
95% CI	[-0.40, 0.56]		[-0.36, 0.68]		[-0.26, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_5_1_1_1_m_fgf23_dose.sas using SAS 9.4

Table 12.4.12.1.2.s7
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0727		0.7806		0.4106	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	31/32	5/5	49/50	10/10
Mean (SD)	30.1 (9.96)	42.6 (13.48)	33.5 (10.51)	41.6 (7.54)	32.3 (10.34)	42.1 (10.31)
Visit 13/ET						
n/N1	17/18	5/5	29/32	4/5	46/50	9/10
Mean (SD)	30.1 (12.30)	37.8 (16.08)	33.1 (14.14)	42.0 (11.58)	32.0 (13.43)	39.7 (13.58)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	1.5 (1.46)	-6.5 (2.91)	-0.5 (1.56)	0.7 (4.29)	0.5 (1.16)	-2.7 (2.62)
95% CI	[-1.55, 4.56]	[-12.63, -0.43]	[-3.70, 2.68]	[-8.07, 9.45]	[-1.85, 2.79]	[-8.00, 2.53]
Diff in LS-Mean [ER-Calcifediol - Placebo]	8.04		-1.20		3.21	
95% CI	[0.89, 15.18]		[-10.57, 8.17]		[-2.67, 9.09]	
p-value	0.0296		0.7956		0.2784	
Hedges' g	0.95		-0.22		0.28	
95% CI	[-0.05, 1.95]		[-1.24, 0.81]		[-0.43, 0.99]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_2_m_egfr_dose.sas using SAS 9.4

Table 12.4.12.1.2.s7
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	30.0 (11.19)	31.5 (10.57)	30.1 (9.40)	31.5 (8.88)	30.1 (10.35)	31.5 (9.74)
Visit 13/ET						
n/N2	106/108	62/63	95/98	56/61	201/206	118/124
Mean (SD)	29.9 (11.74)	31.5 (10.99)	28.1 (10.16)	30.1 (9.92)	29.0 (11.04)	30.8 (10.47)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.70)	-0.1 (0.91)	-1.9 (0.57)	-1.4 (0.74)	-1.2 (0.46)	-0.8 (0.60)
95% CI	[-1.85, 0.90]	[-1.93, 1.67]	[-3.01, -0.77]	[-2.89, 0.03]	[-2.09, -0.30]	[-1.94, 0.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.34		-0.46		-0.43	
95% CI	[-2.61, 1.92]		[-2.30, 1.39]		[-1.91, 1.05]	
p-value	0.7649		0.6239		0.5701	
Hedges' g	-0.01		-0.06		-0.03	
95% CI	[-0.32, 0.30]		[-0.39, 0.27]		[-0.26, 0.19]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_2_m_egfr_dose.sas using SAS 9.4

Table 12.4.15.1.1.s7
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3622		0.1471		0.2412	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	16/18	5/5	23/32	2/5	39/50	7/10
Mean (SD)	0.6 (0.87)	0.1 (0.07)	0.6 (0.83)	4.1 (2.27)	0.6 (0.83)	1.2 (2.17)
Visit 13/ET						
n/N1	13/18	5/5	18/32	2/5	31/50	7/10
Mean (SD)	0.5 (0.61)	0.1 (0.16)	0.9 (1.15)	2.7 (3.31)	0.7 (0.98)	0.9 (1.86)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.11)	-0.2 (0.18)	0.2 (0.25)	1.2 (0.77)	-0.0 (0.15)	0.6 (0.35)
95% CI	[-0.36, 0.11]	[-0.59, 0.18]	[-0.36, 0.69]	[-0.42, 2.81]	[-0.32, 0.29]	[-0.07, 1.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		-1.03		-0.65	
95% CI	[-0.38, 0.55]		[-2.74, 0.68]		[-1.42, 0.12]	
p-value	0.7113		0.2204		0.0959	
Hedges' g	-0.41		-0.96		-0.40	
95% CI	[-1.40, 0.58]		[-2.39, 0.47]		[-1.21, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_15_1_1_m_ua_dose.sas using SAS 9.4

Table 12.4.15.1.1.s7
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	87/108	54/63	74/98	49/61	161/206	103/124
Mean (SD)	0.7 (0.78)	0.7 (0.94)	0.8 (1.01)	0.7 (0.97)	0.7 (0.89)	0.7 (0.95)
Visit 13/ET						
n/N2	87/108	54/63	72/98	40/61	159/206	94/124
Mean (SD)	0.7 (1.04)	0.7 (0.89)	0.8 (1.04)	0.6 (0.74)	0.8 (1.04)	0.7 (0.83)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.0 (0.09)	0.1 (0.08)	-0.1 (0.11)	0.1 (0.05)	-0.0 (0.07)
95% CI	[-0.07, 0.22]	[-0.15, 0.21]	[-0.08, 0.23]	[-0.27, 0.15]	[-0.03, 0.18]	[-0.15, 0.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.14		0.09	
95% CI	[-0.18, 0.28]		[-0.12, 0.40]		[-0.09, 0.26]	
p-value	0.6699		0.2970		0.3286	
Hedges' g	0.08		0.14		0.11	
95% CI	[-0.26, 0.42]		[-0.25, 0.53]		[-0.15, 0.36]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_15_1_1_m_ua_dose.sas using SAS 9.4

Table 12.4.12.1.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1264		0.0100		0.5799	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	9.2 (0.29)	9.2 (0.22)	9.3 (0.30)	9.1 (0.26)	9.2 (0.29)	9.2 (0.24)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	9.3 (0.45)	9.4 (0.35)	9.7 (0.41)	9.1 (0.44)	9.5 (0.47)	9.2 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.2 (0.11)	0.5 (0.07)	-0.0 (0.11)	0.3 (0.05)	0.1 (0.08)
95% CI	[-0.02, 0.33]	[-0.06, 0.41]	[0.31, 0.59]	[-0.25, 0.18]	[0.20, 0.41]	[-0.09, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.49		0.24	
95% CI	[-0.31, 0.27]		[0.23, 0.75]		[0.05, 0.43]	
p-value	0.8806		0.0006		0.0134	
Hedges' g	-0.05		1.56		0.63	
95% CI	[-0.77, 0.67]		[0.70, 2.41]		[0.09, 1.18]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_1_m_dca_vitd.sas using SAS 9.4

Table 12.4.12.1.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	9.2 (0.29)	9.2 (0.29)	9.2 (0.35)	9.3 (0.28)	9.2 (0.32)	9.3 (0.29)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	9.5 (0.51)	9.3 (0.32)	9.5 (0.39)	9.4 (0.55)	9.5 (0.45)	9.4 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.2 (0.03)	0.1 (0.05)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.24, 0.39]	[-0.00, 0.21]	[0.18, 0.32]	[0.03, 0.22]	[0.23, 0.33]	[0.04, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.22		0.12		0.17	
95% CI	[0.09, 0.34]		[0.00, 0.24]		[0.08, 0.26]	
p-value	0.0010		0.0421		0.0001	
Hedges' g	0.57		0.35		0.47	
95% CI	[0.25, 0.89]		[0.02, 0.68]		[0.24, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_1_m_dca_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2914		0.8361		0.5747	
Comparison Baseline vs. EAP	0.6734		0.7150		0.6574	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	3.7 (0.40)	4.0 (0.53)	3.8 (0.52)	3.9 (0.49)	3.7 (0.46)	4.0 (0.51)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	3.9 (0.50)	3.9 (0.82)	4.2 (0.99)	4.1 (0.65)	4.0 (0.79)	4.0 (0.73)
EAP						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	3.8 (0.43)	4.1 (0.51)	4.1 (0.80)	4.1 (0.51)	4.0 (0.67)	4.1 (0.50)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.13)	-0.0 (0.17)	0.4 (0.18)	0.2 (0.27)	0.3 (0.11)	0.1 (0.16)
95% CI	[-0.05, 0.48]	[-0.38, 0.32]	[-0.00, 0.72]	[-0.36, 0.75]	[0.07, 0.51]	[-0.23, 0.39]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.24		0.16		0.21	
95% CI	[-0.21, 0.69]		[-0.50, 0.82]		[-0.17, 0.60]	
p-value	0.2842		0.6154		0.2737	
Hedges' g	0.60		0.22		0.40	
95% CI	[-0.14, 1.33]		[-0.54, 0.98]		[-0.14, 0.93]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.09)	0.2 (0.12)	0.3 (0.13)	0.3 (0.19)	0.2 (0.08)	0.2 (0.11)
95% CI	[-0.13, 0.25]	[-0.04, 0.46]	[0.07, 0.59]	[-0.14, 0.66]	[0.05, 0.36]	[-0.01, 0.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.15		0.07		-0.01	
95% CI	[-0.47, 0.18]		[-0.40, 0.55]		[-0.29, 0.27]	
p-value	0.3592		0.7520		0.9339	
Hedges' g	0.01		0.14		0.11	
95% CI	[-0.71, 0.73]		[-0.62, 0.90]		[-0.42, 0.64]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	3.7 (0.57)	3.8 (0.59)	3.8 (0.57)	3.7 (0.46)	3.7 (0.57)	3.7 (0.53)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	3.9 (0.74)	3.9 (0.64)	4.0 (0.69)	3.7 (0.71)	4.0 (0.71)	3.8 (0.68)
EAP						
n/N2	112/118	58/61	115/123	56/63	227/241	114/124
Mean (SD)	3.9 (0.65)	3.9 (0.59)	4.0 (0.66)	3.7 (0.51)	3.9 (0.65)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.08)	0.2 (0.05)	0.0 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.08, 0.29]	[-0.05, 0.26]	[0.11, 0.33]	[-0.16, 0.16]	[0.13, 0.28]	[-0.06, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.22		0.15	
95% CI	[-0.10, 0.27]		[0.03, 0.41]		[0.02, 0.28]	
p-value	0.3798		0.0238		0.0239	
Hedges' g	0.16		0.30		0.23	
95% CI	[-0.15, 0.48]		[-0.02, 0.63]		[0.00, 0.46]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.06)	0.2 (0.04)	0.0 (0.06)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.10, 0.26]	[-0.00, 0.23]	[0.13, 0.31]	[-0.09, 0.16]	[0.14, 0.26]	[-0.01, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.07		0.18		0.12	
95% CI	[-0.07, 0.21]		[0.03, 0.34]		[0.02, 0.23]	
p-value	0.3417		0.0182		0.0187	
Hedges' g	0.18		0.30		0.24	
95% CI	[-0.14, 0.50]		[-0.02, 0.62]		[0.02, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.5.1.1.1.s8
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2819		0.7717		0.7396	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	15/23	6/11	13/21	4/9	28/44	10/20
Mean (SD)	52.5 (39.57)	44.7 (38.51)	31.7 (25.11)	39.7 (35.14)	42.8 (34.70)	42.7 (35.24)
Visit 13/ET						
n/N1	10/23	3/11	13/21	3/9	23/44	6/20
Mean (SD)	65.3 (33.14)	141.9 (141.27)	71.1 (109.65)	67.2 (44.27)	68.6 (83.76)	104.6 (102.17)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	14.4 (25.16)	101.8 (45.98)	59.2 (45.68)	25.5 (75.26)	37.4 (24.86)	60.9 (42.82)
95% CI	[-42.46, 71.36]	[-2.22, 205.79]	[-46.16, 164.53]	[-148.00, 199.08]	[-14.86, 89.59]	[-29.05, 150.88]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-87.33		33.65		-23.55	
95% CI	[-210.44, 35.77]		[-170.90, 238.19]		[-129.76, 82.65]	
p-value	0.1430		0.7143		0.6469	
Hedges' g	-0.52		0.32		-0.02	
95% CI	[-1.75, 0.70]		[-0.90, 1.54]		[-0.92, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_5_1_1_1_m_fgf23_vitd.sas using SAS 9.4

Table 12.5.1.1.1.s8
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	82/118	35/61	71/123	43/63	153/241	78/124
Mean (SD)	46.3 (52.85)	44.8 (35.08)	35.5 (24.77)	35.4 (29.79)	41.3 (42.43)	39.6 (32.40)
Visit 13/ET						
n/N2	67/118	23/61	62/123	25/63	129/241	48/124
Mean (SD)	49.3 (51.33)	42.7 (30.17)	58.2 (57.18)	61.5 (57.97)	53.6 (54.19)	52.5 (47.24)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	5.3 (6.20)	-5.1 (10.48)	26.2 (9.22)	22.3 (13.66)	15.4 (5.38)	8.5 (8.47)
95% CI	[-7.06, 17.62]	[-25.97, 15.75]	[7.78, 44.61]	[-4.97, 49.62]	[4.76, 26.01]	[-8.25, 25.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	10.39		3.87		6.90	
95% CI	[-13.85, 34.63]		[-29.12, 36.85]		[-12.93, 26.73]	
p-value	0.3959		0.8156		0.4927	
Hedges' g	0.20		0.12		0.14	
95% CI	[-0.29, 0.70]		[-0.39, 0.63]		[-0.22, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_5_1_1_1_m_fgf23_vitd.sas using SAS 9.4

Table 12.4.12.1.2.s8
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0922		0.9818		0.2645	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	28.8 (8.98)	32.8 (13.85)	32.3 (10.10)	26.3 (6.08)	30.5 (9.58)	29.9 (11.29)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	28.5 (10.71)	31.0 (12.85)	30.1 (13.82)	24.3 (7.75)	29.4 (12.31)	28.0 (11.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	2.1 (1.43)	-1.7 (1.90)	-2.6 (1.19)	-1.0 (1.86)	0.0 (0.93)	-1.9 (1.31)
95% CI	[-0.84, 5.03]	[-5.61, 2.20]	[-5.05, -0.15]	[-4.86, 2.76]	[-1.85, 1.86]	[-4.54, 0.73]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.79		-1.55		1.91	
95% CI	[-1.20, 8.79]		[-6.17, 3.06]		[-1.31, 5.13]	
p-value	0.1308		0.4958		0.2394	
Hedges' g	0.64		-0.03		0.29	
95% CI	[-0.10, 1.38]		[-0.79, 0.73]		[-0.24, 0.82]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_2_m_egfr_vitd.sas using SAS 9.4

Table 12.4.12.1.2.s8
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	122/123	63/63	240/241	124/124
Mean (SD)	30.6 (11.44)	32.2 (10.57)	30.7 (9.92)	32.5 (9.80)	30.7 (10.67)	32.4 (10.14)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	30.0 (12.05)	32.2 (11.14)	29.3 (11.09)	31.4 (10.70)	29.7 (11.56)	31.8 (10.89)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.8 (0.68)	-0.2 (0.95)	-1.3 (0.58)	-1.0 (0.84)	-1.1 (0.45)	-0.6 (0.64)
95% CI	[-2.18, 0.49]	[-2.07, 1.68]	[-2.40, -0.12]	[-2.64, 0.66]	[-1.93, -0.18]	[-1.83, 0.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.65		-0.27		-0.47	
95% CI	[-2.95, 1.66]		[-2.28, 1.74]		[-2.00, 1.06]	
p-value	0.5796		0.7909		0.5435	
Hedges' g	-0.05		-0.02		-0.04	
95% CI	[-0.37, 0.27]		[-0.35, 0.30]		[-0.27, 0.19]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_2_m_egfr_vitd.sas using SAS 9.4

Table 12.4.15.1.1.s8
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7682		0.0946		0.1457	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	20/23	9/11	14/21	8/9	34/44	17/20
Mean (SD)	0.7 (0.86)	0.5 (0.87)	1.0 (1.26)	0.6 (0.75)	0.8 (1.03)	0.6 (0.79)
Visit 13/ET						
n/N1	13/23	8/11	13/21	6/9	26/44	14/20
Mean (SD)	0.8 (0.63)	0.2 (0.34)	1.2 (1.42)	0.5 (0.73)	1.0 (1.10)	0.3 (0.53)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.11)	-0.5 (0.14)	0.2 (0.20)	-0.3 (0.29)	0.0 (0.12)	-0.4 (0.17)
95% CI	[-0.33, 0.13]	[-0.77, -0.17]	[-0.20, 0.63]	[-0.96, 0.27]	[-0.20, 0.29]	[-0.72, -0.04]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.37		0.56		0.42	
95% CI	[-0.01, 0.75]		[-0.18, 1.31]		[0.00, 0.84]	
p-value	0.0558		0.1260		0.0480	
Hedges' g	0.17		0.75		0.47	
95% CI	[-0.67, 1.02]		[-0.20, 1.71]		[-0.17, 1.12]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_15_1_1_m_ua_vitd.sas using SAS 9.4

Table 12.4.15.1.1.s8
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	96/118	53/61	96/123	47/63	192/241	100/124
Mean (SD)	0.6 (0.75)	0.7 (0.91)	0.7 (1.00)	0.9 (1.27)	0.7 (0.88)	0.8 (1.09)
Visit 13/ET						
n/N2	92/118	52/61	84/123	37/63	176/241	89/124
Mean (SD)	0.7 (1.15)	0.7 (0.91)	0.9 (1.30)	1.0 (1.73)	0.8 (1.22)	0.8 (1.31)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.10)	0.1 (0.11)	0.3 (0.17)	0.1 (0.07)	0.2 (0.09)
95% CI	[-0.05, 0.26]	[-0.13, 0.28]	[-0.10, 0.34]	[-0.08, 0.59]	[-0.02, 0.24]	[-0.02, 0.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		-0.13		-0.05	
95% CI	[-0.23, 0.28]		[-0.53, 0.27]		[-0.28, 0.18]	
p-value	0.8386		0.5220		0.6588	
Hedges' g	0.04		-0.13		-0.04	
95% CI	[-0.30, 0.38]		[-0.52, 0.26]		[-0.30, 0.21]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_15_1_1_m_ua_vitd.sas using SAS 9.4

Table 12.4.12.1.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5106		0.4089		0.9475	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	9.2 (0.29)	9.2 (0.29)	9.2 (0.32)	9.3 (0.23)	9.2 (0.31)	9.3 (0.26)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	9.5 (0.40)	9.3 (0.34)	9.4 (0.41)	9.4 (0.60)	9.5 (0.40)	9.3 (0.47)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.2 (0.05)	0.1 (0.07)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.19, 0.35]	[-0.02, 0.19]	[0.14, 0.33]	[-0.05, 0.24]	[0.19, 0.31]	[0.01, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.14		0.16	
95% CI	[0.05, 0.32]		[-0.03, 0.31]		[0.05, 0.27]	
p-value	0.0086		0.1002		0.0043	
Hedges' g	0.58		0.38		0.48	
95% CI	[0.17, 0.98]		[-0.06, 0.82]		[0.18, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_1_m_dca_bl25d.sas using SAS 9.4

Table 12.4.12.1.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	9.2 (0.28)	9.2 (0.28)	9.3 (0.37)	9.2 (0.32)	9.2 (0.33)	9.2 (0.30)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	9.5 (0.59)	9.4 (0.30)	9.6 (0.37)	9.3 (0.49)	9.6 (0.49)	9.3 (0.41)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.08)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.21, 0.42]	[-0.01, 0.31]	[0.25, 0.42]	[-0.02, 0.21]	[0.26, 0.39]	[0.03, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.24		0.20	
95% CI	[-0.03, 0.36]		[0.10, 0.39]		[0.08, 0.32]	
p-value	0.0926		0.0009		0.0010	
Hedges' g	0.38		0.64		0.50	
95% CI	[-0.05, 0.81]		[0.22, 1.06]		[0.20, 0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_1_m_dca_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9616		0.2478		0.3998	
Comparison Baseline vs. EAP	0.5208		0.7920		0.5386	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	3.7 (0.51)	3.8 (0.61)	3.8 (0.61)	3.7 (0.40)	3.8 (0.57)	3.7 (0.52)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	3.9 (0.67)	3.8 (0.65)	4.1 (0.84)	3.9 (0.77)	4.0 (0.76)	3.8 (0.70)
EAP						
n/N1	64/68	39/40	66/70	31/36	130/138	70/76
Mean (SD)	3.9 (0.52)	3.9 (0.59)	4.1 (0.76)	3.8 (0.56)	4.0 (0.65)	3.8 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.0 (0.09)	0.3 (0.08)	0.2 (0.12)	0.2 (0.05)	0.1 (0.08)
95% CI	[0.05, 0.34]	[-0.14, 0.24]	[0.10, 0.41]	[-0.05, 0.43]	[0.12, 0.33]	[-0.04, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.14		0.07		0.12	
95% CI	[-0.10, 0.38]		[-0.21, 0.36]		[-0.07, 0.30]	
p-value	0.2367		0.6209		0.2102	
Hedges' g	0.22		0.09		0.17	
95% CI	[-0.18, 0.62]		[-0.35, 0.53]		[-0.12, 0.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.06)	0.3 (0.06)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.05, 0.25]	[0.00, 0.25]	[0.13, 0.38]	[-0.07, 0.30]	[0.13, 0.29]	[0.01, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.15		0.09	
95% CI	[-0.14, 0.19]		[-0.08, 0.37]		[-0.04, 0.23]	
p-value	0.7594		0.1971		0.1774	
Hedges' g	0.06		0.23		0.16	
95% CI	[-0.33, 0.46]		[-0.19, 0.66]		[-0.13, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	3.7 (0.58)	3.9 (0.55)	3.7 (0.51)	3.7 (0.53)	3.7 (0.54)	3.8 (0.55)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	3.9 (0.74)	4.0 (0.67)	3.9 (0.63)	3.6 (0.64)	3.9 (0.68)	3.8 (0.68)
EAP						
n/N2	67/73	30/32	70/74	34/36	137/147	64/68
Mean (SD)	3.9 (0.71)	4.0 (0.57)	3.9 (0.61)	3.7 (0.50)	3.9 (0.66)	3.9 (0.55)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.10)	0.2 (0.07)	-0.1 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.06, 0.33]	[-0.09, 0.32]	[0.08, 0.36]	[-0.28, 0.11]	[0.11, 0.30]	[-0.12, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.31		0.18	
95% CI	[-0.17, 0.33]		[0.07, 0.55]		[0.01, 0.35]	
p-value	0.5107		0.0125		0.0424	
Hedges' g	0.23		0.45		0.35	
95% CI	[-0.20, 0.66]		[0.04, 0.86]		[0.06, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.09)	0.2 (0.06)	0.0 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.07, 0.30]	[-0.07, 0.27]	[0.10, 0.32]	[-0.12, 0.19]	[0.12, 0.27]	[-0.04, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.18		0.12	
95% CI	[-0.12, 0.29]		[-0.02, 0.37]		[-0.02, 0.26]	
p-value	0.4150		0.0754		0.1010	
Hedges' g	0.25		0.31		0.29	
95% CI	[-0.17, 0.68]		[-0.10, 0.72]		[-0.01, 0.59]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.5.1.1.1.s9
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5361		0.5988		0.4660	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	45/68	23/40	39/70	24/36	84/138	47/76
Mean (SD)	41.8 (33.52)	46.0 (32.41)	31.5 (20.83)	35.8 (30.76)	37.0 (28.65)	40.8 (31.66)
Visit 13/ET						
n/N1	39/68	16/40	41/70	17/36	80/138	33/76
Mean (SD)	37.3 (28.30)	53.9 (71.30)	58.6 (75.13)	62.6 (66.28)	48.2 (57.94)	58.3 (67.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.8 (8.00)	12.8 (12.17)	32.2 (15.00)	27.0 (21.27)	16.7 (8.18)	19.1 (11.96)
95% CI	[-15.35, 16.86]	[-11.73, 37.27]	[1.81, 62.51]	[-16.03, 70.00]	[0.45, 32.96]	[-4.71, 42.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-12.01		5.18		-2.36	
95% CI	[-41.66, 17.64]		[-47.63, 57.98]		[-31.35, 26.63]	
p-value	0.4191		0.8439		0.8718	
Hedges' g	-0.08		0.07		-0.01	
95% CI	[-0.68, 0.52]		[-0.56, 0.70]		[-0.44, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_5_1_1_1_m_fgf23_bl25d.sas using SAS 9.4

Table 12.5.1.1.1.s9
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	52/73	18/32	45/74	23/36	97/147	41/68
Mean (SD)	51.9 (62.11)	43.2 (39.16)	37.8 (27.54)	35.7 (29.61)	45.4 (49.47)	39.0 (33.88)
Visit 13/ET						
n/N2	38/73	10/32	34/74	11/36	72/147	21/68
Mean (SD)	65.7 (61.53)	54.6 (32.99)	62.7 (60.15)	61.4 (37.90)	64.3 (60.47)	58.2 (34.93)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	12.9 (10.08)	-2.8 (19.89)	30.1 (11.41)	16.3 (18.45)	21.3 (7.68)	5.2 (13.64)
95% CI	[-7.44, 33.29]	[-42.92, 37.41]	[6.87, 53.31]	[-21.20, 53.87]	[6.00, 36.61]	[-21.93, 32.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	15.68		13.75		16.07	
95% CI	[-29.36, 60.71]		[-30.49, 57.98]		[-15.13, 47.26]	
p-value	0.4860		0.5315		0.3082	
Hedges' g	0.22		0.32		0.25	
95% CI	[-0.50, 0.94]		[-0.39, 1.04]		[-0.27, 0.76]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_5_1_1_1_m_fgf23_bl25d.sas using SAS 9.4

Table 12.4.12.1.2.s9
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0613		0.5428		0.0820	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	30.4 (11.58)	32.6 (12.13)	31.1 (10.54)	31.1 (9.08)	30.7 (11.03)	31.9 (10.75)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	30.0 (12.49)	30.8 (11.67)	29.1 (11.70)	27.7 (9.62)	29.5 (12.06)	29.5 (10.88)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.99)	-1.4 (1.29)	-1.5 (0.72)	-2.0 (1.09)	-0.6 (0.62)	-1.8 (0.87)
95% CI	[-1.81, 2.12]	[-3.92, 1.19]	[-2.90, -0.05]	[-4.17, 0.18]	[-1.83, 0.60]	[-3.49, -0.05]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.52		0.52		1.15	
95% CI	[-1.71, 4.75]		[-2.08, 3.12]		[-0.96, 3.26]	
p-value	0.3532		0.6934		0.2833	
Hedges' g	0.26		0.08		0.18	
95% CI	[-0.14, 0.66]		[-0.36, 0.52]		[-0.12, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_2_m_egfr_bl25d.sas using SAS 9.4

Table 12.4.12.1.2.s9
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	73/74	36/36	146/147	68/68
Mean (SD)	30.3 (10.64)	32.0 (9.64)	30.9 (9.37)	32.4 (10.19)	30.6 (10.00)	32.2 (9.87)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	29.6 (11.28)	33.5 (10.92)	29.8 (11.40)	32.6 (10.94)	29.7 (11.30)	33.0 (10.86)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.0 (0.72)	0.9 (1.07)	-1.3 (0.77)	-0.6 (1.08)	-1.2 (0.53)	0.2 (0.76)
95% CI	[-2.47, 0.38]	[-1.23, 3.03]	[-2.79, 0.26]	[-2.72, 1.58]	[-2.19, -0.12]	[-1.34, 1.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-1.95		-0.70		-1.32	
95% CI	[-4.51, 0.62]		[-3.34, 1.95]		[-3.15, 0.51]	
p-value	0.1349		0.6023		0.1551	
Hedges' g	-0.30		-0.11		-0.20	
95% CI	[-0.73, 0.12]		[-0.52, 0.30]		[-0.49, 0.10]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_2_m_egfr_bl25d.sas using SAS 9.4

Table 12.4.15.1.1.s9
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8698		0.3591		0.3822	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	60/68	38/40	58/70	28/36	118/138	66/76
Mean (SD)	0.6 (0.74)	0.7 (0.92)	0.9 (1.19)	1.0 (1.36)	0.7 (0.99)	0.8 (1.13)
Visit 13/ET						
n/N1	58/68	34/40	50/70	20/36	108/138	54/76
Mean (SD)	0.6 (1.03)	0.6 (0.83)	1.1 (1.56)	0.8 (0.80)	0.8 (1.31)	0.7 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.09)	-0.0 (0.12)	0.2 (0.12)	-0.0 (0.20)	0.1 (0.07)	-0.0 (0.11)
95% CI	[-0.15, 0.21]	[-0.25, 0.22]	[-0.10, 0.40]	[-0.41, 0.40]	[-0.05, 0.24]	[-0.23, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.15		0.10	
95% CI	[-0.24, 0.34]		[-0.32, 0.63]		[-0.16, 0.37]	
p-value	0.7392		0.5202		0.4391	
Hedges' g	0.08		0.16		0.13	
95% CI	[-0.34, 0.50]		[-0.36, 0.69]		[-0.20, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_15_1_1_m_ua_bl25d.sas using SAS 9.4

Table 12.4.15.1.1.s9
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	56/73	24/32	52/74	27/36	108/147	51/68
Mean (SD)	0.6 (0.80)	0.6 (0.87)	0.6 (0.83)	0.7 (1.03)	0.6 (0.81)	0.7 (0.95)
Visit 13/ET						
n/N2	47/73	26/32	47/74	23/36	94/147	49/68
Mean (SD)	0.8 (1.18)	0.6 (0.94)	0.7 (0.99)	1.0 (2.13)	0.8 (1.08)	0.8 (1.60)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.12)	0.1 (0.16)	0.1 (0.16)	0.3 (0.22)	0.1 (0.10)	0.2 (0.14)
95% CI	[-0.12, 0.35]	[-0.24, 0.40]	[-0.20, 0.44]	[-0.14, 0.75]	[-0.08, 0.31]	[-0.07, 0.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		-0.18		-0.08	
95% CI	[-0.37, 0.43]		[-0.73, 0.36]		[-0.42, 0.25]	
p-value	0.8723		0.5021		0.6160	
Hedges' g	0.03		-0.17		-0.08	
95% CI	[-0.45, 0.51]		[-0.67, 0.33]		[-0.43, 0.26]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_15_1_1_m_ua_bl25d.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalyse - Sicherheitsendpunkte Sicherheits-relevante sHPT-assoziierte Parameter (PP-Population)

Folgende Daten werden für die PP-Population

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum
- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.12.1.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5791		0.6380		0.9837	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	9.2 (0.29)	9.3 (0.27)	9.2 (0.32)	9.2 (0.30)	9.2 (0.30)	9.2 (0.28)
Visit 13/ET						
n/N1	51/51	28/28	40/40	25/26	91/91	53/54
Mean (SD)	9.5 (0.38)	9.3 (0.37)	9.5 (0.44)	9.3 (0.52)	9.5 (0.41)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.06)	0.2 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.14, 0.34]	[-0.08, 0.19]	[0.21, 0.43]	[0.02, 0.30]	[0.21, 0.36]	[-0.00, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.16		0.19	
95% CI	[0.02, 0.36]		[-0.02, 0.35]		[0.07, 0.31]	
p-value	0.0257		0.0749		0.0029	
Hedges' g	0.57		0.46		0.52	
95% CI	[0.11, 1.04]		[-0.04, 0.96]		[0.17, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_m_dca_age_pp.sas using SAS 9.4

Table 12.4.12.1.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	9.2 (0.26)	9.2 (0.28)	9.2 (0.31)	9.3 (0.25)	9.2 (0.29)	9.3 (0.26)
Visit 13/ET						
n/N2	64/64	33/34	77/79	32/34	141/143	65/68
Mean (SD)	9.5 (0.42)	9.4 (0.29)	9.5 (0.34)	9.4 (0.58)	9.5 (0.38)	9.4 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.2 (0.05)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.21, 0.36]	[0.06, 0.28]	[0.21, 0.37]	[-0.05, 0.20]	[0.23, 0.34]	[0.04, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.21		0.16	
95% CI	[-0.02, 0.25]		[0.06, 0.37]		[0.06, 0.27]	
p-value	0.0862		0.0063		0.0015	
Hedges' g	0.39		0.62		0.51	
95% CI	[-0.03, 0.81]		[0.20, 1.03]		[0.21, 0.81]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_m_dca_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7973		0.4512		0.7277	
Comparison Baseline vs. EAP	0.3680		0.5516		0.3211	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	3.8 (0.52)	4.0 (0.57)	3.9 (0.63)	3.6 (0.49)	3.8 (0.57)	3.8 (0.56)
Visit 13/ET						
n/N1	51/51	28/28	40/40	25/26	91/91	53/54
Mean (SD)	3.9 (0.68)	4.0 (0.66)	4.2 (0.91)	3.7 (0.91)	4.0 (0.80)	3.8 (0.80)
EAP						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	4.0 (0.56)	4.0 (0.50)	4.2 (0.79)	3.7 (0.66)	4.0 (0.68)	3.9 (0.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.0 (0.11)	0.3 (0.12)	0.0 (0.15)	0.2 (0.07)	0.0 (0.09)
95% CI	[-0.10, 0.23]	[-0.17, 0.26]	[0.09, 0.56]	[-0.30, 0.30]	[0.07, 0.34]	[-0.17, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.32		0.20	
95% CI	[-0.26, 0.29]		[-0.06, 0.71]		[-0.02, 0.43]	
p-value	0.8933		0.0996		0.0809	
Hedges' g	0.13		0.41		0.26	
95% CI	[-0.33, 0.59]		[-0.09, 0.91]		[-0.07, 0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.1 (0.08)	0.3 (0.09)	0.0 (0.11)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.01, 0.24]	[-0.07, 0.24]	[0.09, 0.45]	[-0.20, 0.25]	[0.10, 0.30]	[-0.09, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.24		0.16	
95% CI	[-0.15, 0.23]		[-0.05, 0.53]		[-0.00, 0.33]	
p-value	0.6807		0.0967		0.0544	
Hedges' g	0.22		0.36		0.29	
95% CI	[-0.24, 0.68]		[-0.13, 0.85]		[-0.05, 0.62]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	3.7 (0.55)	3.7 (0.57)	3.7 (0.54)	3.6 (0.40)	3.7 (0.54)	3.6 (0.49)
Visit 13/ET						
n/N2	64/64	33/34	77/79	32/34	141/143	65/68
Mean (SD)	3.9 (0.73)	3.7 (0.63)	3.9 (0.59)	3.8 (0.55)	3.9 (0.66)	3.8 (0.58)
EAP						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	3.8 (0.66)	3.8 (0.62)	4.0 (0.59)	3.8 (0.42)	3.9 (0.63)	3.8 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.10)	0.2 (0.06)	0.1 (0.09)	0.2 (0.05)	0.1 (0.07)
95% CI	[0.11, 0.39]	[-0.08, 0.31]	[0.10, 0.33]	[-0.08, 0.27]	[0.14, 0.32]	[-0.03, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.12		0.12	
95% CI	[-0.11, 0.37]		[-0.09, 0.33]		[-0.03, 0.28]	
p-value	0.2860		0.2546		0.1254	
Hedges' g	0.21		0.16		0.18	
95% CI	[-0.21, 0.63]		[-0.25, 0.57]		[-0.11, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.2 (0.07)	0.2 (0.05)	0.1 (0.07)	0.2 (0.03)	0.2 (0.05)
95% CI	[0.06, 0.26]	[0.04, 0.32]	[0.15, 0.33]	[-0.00, 0.28]	[0.13, 0.27]	[0.07, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.10		0.03	
95% CI	[-0.20, 0.15]		[-0.07, 0.27]		[-0.09, 0.15]	
p-value	0.7592		0.2405		0.5992	
Hedges' g	-0.06		0.17		0.06	
95% CI	[-0.48, 0.35]		[-0.23, 0.57]		[-0.22, 0.35]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.5.1.1.1.s1.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2080		0.7707		0.8212	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	34/51	15/28	24/40	17/26	58/91	32/54
Mean (SD)	43.3 (35.35)	35.9 (19.94)	39.3 (31.56)	31.6 (20.63)	41.6 (33.61)	33.6 (20.10)
Visit 13/ET						
n/N1	30/51	12/28	26/40	12/26	56/91	24/54
Mean (SD)	43.1 (31.25)	34.0 (28.77)	76.2 (93.03)	65.2 (63.69)	58.5 (68.75)	49.6 (50.88)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	5.6 (5.31)	-12.5 (8.42)	53.2 (23.91)	32.3 (36.31)	28.0 (10.55)	12.4 (16.22)
95% CI	[-5.25, 16.40]	[-29.61, 4.68]	[3.74, 102.66]	[-42.86, 107.37]	[6.92, 49.17]	[-20.08, 44.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	18.04		20.94		15.64	
95% CI	[-2.26, 38.35]		[-70.21, 112.10]		[-23.17, 54.46]	
p-value	0.0797		0.6390		0.4229	
Hedges' g	0.70		0.03		0.16	
95% CI	[-0.04, 1.43]		[-0.77, 0.84]		[-0.39, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_5_1_1_1_m_fgf23_age_pp.sas using SAS 9.4

Table 12.5.1.1.1.s1.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	46/64	20/34	45/79	22/34	91/143	42/68
Mean (SD)	50.3 (64.09)	48.2 (43.41)	31.9 (21.12)	36.1 (29.51)	41.2 (48.55)	41.8 (36.83)
Visit 13/ET						
n/N2	39/64	10/34	41/79	13/34	80/143	23/68
Mean (SD)	52.5 (56.68)	52.2 (33.02)	52.1 (51.21)	61.5 (55.49)	52.3 (53.60)	57.5 (46.34)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	3.4 (9.12)	1.0 (17.31)	25.5 (10.24)	20.2 (15.72)	13.4 (6.87)	12.3 (11.70)
95% CI	[-15.00, 21.80]	[-33.87, 35.96]	[4.79, 46.20]	[-11.60, 51.93]	[-0.28, 27.05]	[-10.95, 35.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	2.35		5.33		1.07	
95% CI	[-37.12, 41.82]		[-32.99, 43.65]		[-25.93, 28.08]	
p-value	0.9050		0.7800		0.9372	
Hedges' g	0.05		0.19		0.07	
95% CI	[-0.64, 0.74]		[-0.45, 0.83]		[-0.40, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_5_1_1_1_m_fgf23_age_pp.sas using SAS 9.4

Table 12.4.12.1.2.s1.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3102		0.9354		0.4909	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	29.9 (12.65)	31.9 (10.54)	29.6 (10.23)	32.2 (9.11)	29.8 (11.59)	32.1 (9.78)
Visit 13/ET						
n/N1	51/51	28/28	40/40	25/26	91/91	53/54
Mean (SD)	29.1 (12.38)	32.0 (11.88)	29.1 (13.80)	31.1 (10.71)	29.1 (12.95)	31.6 (11.24)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.0 (0.98)	0.3 (1.32)	-0.4 (1.14)	-0.7 (1.44)	-0.7 (0.76)	-0.2 (0.99)
95% CI	[-2.90, 0.99]	[-2.35, 2.90]	[-2.71, 1.84]	[-3.58, 2.18]	[-2.22, 0.77]	[-2.12, 1.78]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-1.23		0.27		-0.56	
95% CI	[-4.50, 2.04]		[-3.42, 3.95]		[-3.02, 1.90]	
p-value	0.4555		0.8855		0.6537	
Hedges' g	-0.13		0.01		-0.06	
95% CI	[-0.58, 0.33]		[-0.48, 0.51]		[-0.40, 0.27]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_2_m_egfr_age_pp.sas using SAS 9.4

Table 12.4.12.1.2.s1.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population

Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	30.6 (9.56)	34.5 (11.48)	31.4 (9.05)	32.7 (9.49)	31.0 (9.26)	33.6 (10.49)
Visit 13/ET						
n/N2	64/64	33/34	77/79	32/34	141/143	65/68
Mean (SD)	30.7 (11.36)	33.6 (11.16)	29.2 (9.75)	30.7 (10.75)	29.9 (10.50)	32.2 (10.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.94)	-0.9 (1.32)	-1.8 (0.61)	-1.7 (0.94)	-1.0 (0.54)	-1.3 (0.80)
95% CI	[-1.98, 1.75]	[-3.51, 1.72]	[-3.04, -0.64]	[-3.56, 0.17]	[-2.03, 0.12]	[-2.92, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.78		-0.15		0.38	
95% CI	[-2.46, 4.02]		[-2.37, 2.07]		[-1.54, 2.30]	
p-value	0.6347		0.8949		0.6941	
Hedges' g	0.19		-0.01		0.09	
95% CI	[-0.22, 0.61]		[-0.42, 0.40]		[-0.20, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_2_m_egfr_age_pp.sas using SAS 9.4

Table 12.4.15.1.1.s1.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0149		0.9211		0.0812	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	42/51	22/28	35/40	22/26	77/91	44/54
Mean (SD)	0.6 (0.68)	0.7 (0.70)	0.8 (1.11)	1.0 (1.47)	0.7 (0.90)	0.9 (1.14)
Visit 13/ET						
n/N1	43/51	24/28	34/40	20/26	77/91	44/54
Mean (SD)	0.5 (0.55)	0.9 (1.01)	0.9 (1.10)	0.6 (0.70)	0.7 (0.85)	0.7 (0.88)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.09)	0.2 (0.12)	0.1 (0.11)	-0.1 (0.15)	0.0 (0.07)	0.0 (0.09)
95% CI	[-0.25, 0.09]	[-0.05, 0.42]	[-0.13, 0.33]	[-0.39, 0.20]	[-0.13, 0.15]	[-0.13, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.26		0.19		-0.04	
95% CI	[-0.55, 0.03]		[-0.18, 0.56]		[-0.27, 0.19]	
p-value	0.0758		0.3131		0.7406	
Hedges' g	-0.40		0.17		-0.12	
95% CI	[-0.90, 0.10]		[-0.38, 0.72]		[-0.49, 0.25]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_15_1_1_m_ua_age_pp.sas using SAS 9.4

Table 12.4.15.1.1.s1.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	51/64	31/34	54/79	24/34	105/143	55/68
Mean (SD)	0.7 (0.87)	0.6 (1.11)	0.6 (0.85)	0.6 (0.95)	0.6 (0.85)	0.6 (1.03)
Visit 13/ET						
n/N2	50/64	30/34	52/79	19/34	102/143	49/68
Mean (SD)	0.8 (1.29)	0.5 (0.75)	0.8 (1.03)	0.6 (0.80)	0.8 (1.16)	0.5 (0.77)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.10)	-0.1 (0.13)	0.1 (0.11)	-0.0 (0.18)	0.2 (0.07)	-0.1 (0.11)
95% CI	[-0.00, 0.39]	[-0.37, 0.14]	[-0.09, 0.33]	[-0.39, 0.33]	[0.01, 0.30]	[-0.29, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.31		0.15		0.24	
95% CI	[-0.01, 0.64]		[-0.27, 0.57]		[-0.02, 0.50]	
p-value	0.0571		0.4733		0.0734	
Hedges' g	0.44		0.21		0.33	
95% CI	[-0.02, 0.89]		[-0.33, 0.74]		[-0.01, 0.68]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_15_1_1_m_ua_age_pp.sas using SAS 9.4

Table 12.4.12.1.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9594		0.2631		0.4478	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	9.2 (0.27)	9.3 (0.22)	9.3 (0.31)	9.3 (0.26)	9.3 (0.30)	9.3 (0.24)
Visit 13/ET						
n/N1	59/59	28/29	58/59	30/31	117/118	58/60
Mean (SD)	9.5 (0.43)	9.4 (0.35)	9.7 (0.37)	9.5 (0.61)	9.6 (0.41)	9.4 (0.50)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.19, 0.37]	[-0.02, 0.25]	[0.21, 0.41]	[0.02, 0.30]	[0.23, 0.36]	[0.04, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.16		0.15		0.16	
95% CI	[0.00, 0.32]		[-0.02, 0.32]		[0.04, 0.27]	
p-value	0.0441		0.0898		0.0081	
Hedges' g	0.49		0.38		0.43	
95% CI	[0.03, 0.94]		[-0.06, 0.82]		[0.11, 0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_1_m_dca_sex_pp.sas using SAS 9.4

Table 12.4.12.1.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	9.2 (0.27)	9.2 (0.32)	9.1 (0.29)	9.2 (0.27)	9.1 (0.28)	9.2 (0.29)
Visit 13/ET						
n/N2	56/56	33/33	59/60	27/29	115/116	60/62
Mean (SD)	9.4 (0.37)	9.3 (0.31)	9.4 (0.35)	9.2 (0.44)	9.4 (0.36)	9.3 (0.38)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.06)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.16, 0.33]	[0.01, 0.23]	[0.21, 0.38]	[-0.07, 0.18]	[0.21, 0.33]	[0.00, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.24		0.19	
95% CI	[-0.01, 0.27]		[0.09, 0.39]		[0.09, 0.29]	
p-value	0.0643		0.0020		0.0003	
Hedges' g	0.47		0.74		0.60	
95% CI	[0.04, 0.90]		[0.28, 1.21]		[0.29, 0.92]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_1_m_dca_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0503		0.1855		0.6962	
Comparison Baseline vs. EAP	0.2681		0.3056		0.9477	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	3.8 (0.52)	3.9 (0.61)	3.8 (0.43)	3.7 (0.43)	3.8 (0.47)	3.8 (0.53)
Visit 13/ET						
n/N1	59/59	28/29	58/59	30/31	117/118	58/60
Mean (SD)	4.0 (0.65)	3.8 (0.55)	4.0 (0.57)	3.8 (0.73)	4.0 (0.61)	3.8 (0.64)
EAP						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	4.0 (0.60)	4.0 (0.54)	4.0 (0.47)	3.8 (0.55)	4.0 (0.54)	3.9 (0.55)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	-0.1 (0.09)	0.1 (0.07)	0.1 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.08, 0.34]	[-0.25, 0.12]	[-0.00, 0.28]	[-0.11, 0.28]	[0.08, 0.27]	[-0.12, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.28		0.05		0.17	
95% CI	[0.05, 0.50]		[-0.19, 0.29]		[0.00, 0.33]	
p-value	0.0158		0.6771		0.0455	
Hedges' g	0.54		0.04		0.28	
95% CI	[0.09, 1.00]		[-0.40, 0.48]		[-0.03, 0.59]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.05)
95% CI	[0.11, 0.30]	[-0.02, 0.24]	[0.06, 0.26]	[-0.04, 0.23]	[0.11, 0.25]	[0.01, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.06		0.07	
95% CI	[-0.07, 0.25]		[-0.11, 0.23]		[-0.04, 0.19]	
p-value	0.2682		0.4645		0.2219	
Hedges' g	0.26		0.08		0.17	
95% CI	[-0.18, 0.70]		[-0.36, 0.51]		[-0.14, 0.48]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	3.6 (0.55)	3.7 (0.58)	3.7 (0.68)	3.5 (0.43)	3.7 (0.62)	3.6 (0.52)
Visit 13/ET						
n/N2	56/56	33/33	59/60	27/29	115/116	60/62
Mean (SD)	3.7 (0.74)	3.9 (0.72)	4.1 (0.86)	3.6 (0.71)	3.9 (0.82)	3.8 (0.73)
EAP						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	3.7 (0.60)	3.9 (0.60)	4.1 (0.82)	3.6 (0.51)	3.9 (0.74)	3.8 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.2 (0.11)	0.4 (0.09)	0.0 (0.13)	0.2 (0.06)	0.1 (0.08)
95% CI	[-0.05, 0.29]	[-0.01, 0.43]	[0.19, 0.54]	[-0.25, 0.26]	[0.12, 0.36]	[-0.06, 0.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.09		0.37		0.14	
95% CI	[-0.37, 0.18]		[0.05, 0.68]		[-0.06, 0.35]	
p-value	0.5010		0.0220		0.1739	
Hedges' g	-0.08		0.47		0.19	
95% CI	[-0.51, 0.35]		[0.01, 0.92]		[-0.12, 0.50]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.3 (0.07)	0.1 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[-0.04, 0.20]	[0.00, 0.31]	[0.20, 0.48]	[-0.12, 0.28]	[0.12, 0.30]	[-0.01, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.08		0.26		0.10	
95% CI	[-0.27, 0.12]		[0.01, 0.51]		[-0.06, 0.25]	
p-value	0.4398		0.0409		0.2127	
Hedges' g	-0.08		0.40		0.18	
95% CI	[-0.51, 0.34]		[-0.04, 0.84]		[-0.13, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.5.1.1.1.s2.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3829		0.2230		0.3885	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	35/59	16/29	33/59	21/31	68/118	37/60
Mean (SD)	49.2 (39.35)	38.9 (39.01)	32.9 (21.31)	34.5 (28.30)	41.3 (32.71)	36.4 (32.92)
Visit 13/ET						
n/N1	34/59	5/29	31/59	14/31	65/118	19/60
Mean (SD)	49.6 (44.12)	29.2 (31.81)	54.3 (52.79)	72.0 (54.65)	51.8 (48.12)	60.7 (52.51)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	11.4 (8.00)	-12.6 (19.61)	22.9 (11.25)	39.0 (15.92)	17.2 (6.83)	13.0 (13.13)
95% CI	[-4.90, 27.71]	[-52.57, 27.32]	[-0.08, 45.89]	[6.50, 71.51]	[3.51, 30.81]	[-13.27, 39.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	24.03		-16.09		4.20	
95% CI	[-19.12, 67.19]		[-55.90, 23.72]		[-25.37, 33.78]	
p-value	0.2650		0.4156		0.7774	
Hedges' g	0.53		-0.30		-0.12	
95% CI	[-0.40, 1.47]		[-1.01, 0.41]		[-0.68, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_5_1_1_1_m_fgf23_sex_pp.sas using SAS 9.4

Table 12.5.1.1.1.s2.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	45/56	19/33	36/60	18/29	81/116	37/62
Mean (SD)	45.9 (62.91)	46.3 (32.80)	35.9 (28.64)	33.7 (23.35)	41.4 (50.61)	40.2 (28.92)
Visit 13/ET						
n/N2	35/56	17/33	36/60	11/29	71/116	28/62
Mean (SD)	47.4 (50.76)	46.1 (31.19)	67.6 (83.50)	52.2 (63.56)	57.6 (69.58)	48.5 (45.63)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.6 (8.48)	-5.5 (12.20)	44.0 (17.49)	16.7 (28.22)	20.5 (9.09)	4.5 (13.95)
95% CI	[-18.70, 15.52]	[-30.08, 19.11]	[8.38, 79.53]	[-40.73, 74.09]	[2.35, 38.56]	[-23.33, 32.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.89		27.27		15.99	
95% CI	[-26.07, 33.85]		[-40.30, 94.85]		[-17.17, 49.16]	
p-value	0.7947		0.4175		0.3399	
Hedges' g	0.04		0.33		0.20	
95% CI	[-0.57, 0.64]		[-0.39, 1.04]		[-0.27, 0.66]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_5_1_1_1_m_fgf23_sex_pp.sas using SAS 9.4

Table 12.4.12.1.2.s2.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7859		0.7624		0.6923	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	29.8 (10.57)	33.0 (11.64)	32.0 (10.53)	34.2 (9.80)	30.9 (10.56)	33.6 (10.65)
Visit 13/ET						
n/N1	59/59	28/29	58/59	30/31	117/118	58/60
Mean (SD)	30.2 (11.79)	33.3 (11.60)	30.7 (13.00)	32.9 (10.75)	30.5 (12.36)	33.1 (11.07)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.85)	0.0 (1.24)	-0.9 (0.89)	-1.1 (1.24)	-0.3 (0.62)	-0.6 (0.88)
95% CI	[-1.41, 1.98]	[-2.43, 2.51]	[-2.69, 0.85]	[-3.59, 1.35]	[-1.53, 0.91]	[-2.29, 1.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.25		0.20		0.25	
95% CI	[-2.77, 3.26]		[-2.85, 3.24]		[-1.88, 2.38]	
p-value	0.8718		0.8975		0.8176	
Hedges' g	0.09		0.02		0.06	
95% CI	[-0.35, 0.54]		[-0.41, 0.46]		[-0.25, 0.38]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_2_m_egfr_sex_pp.sas using SAS 9.4

Table 12.4.12.1.2.s2.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	30.8 (11.48)	33.6 (10.68)	29.6 (8.19)	30.7 (8.42)	30.2 (9.89)	32.2 (9.72)
Visit 13/ET						
n/N2	56/56	33/33	59/60	27/29	115/116	60/62
Mean (SD)	29.8 (11.91)	32.5 (11.45)	27.6 (9.03)	28.6 (10.24)	28.7 (10.54)	30.7 (11.00)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.3 (1.05)	-0.7 (1.37)	-1.8 (0.70)	-1.4 (1.04)	-1.5 (0.63)	-1.1 (0.88)
95% CI	[-3.36, 0.81]	[-3.47, 1.97]	[-3.20, -0.41]	[-3.45, 0.67]	[-2.77, -0.28]	[-2.83, 0.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.52		-0.42		-0.43	
95% CI	[-3.96, 2.92]		[-2.90, 2.07]		[-2.57, 1.71]	
p-value	0.7630		0.7394		0.6944	
Hedges' g	0.01		-0.07		-0.03	
95% CI	[-0.42, 0.43]		[-0.52, 0.38]		[-0.34, 0.28]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_2_m_egfr_sex_pp.sas using SAS 9.4

Table 12.4.15.1.1.s2.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4859		0.5106		0.3162	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	46/59	21/29	38/59	20/31	84/118	41/60
Mean (SD)	0.6 (0.84)	0.6 (0.70)	0.6 (0.87)	0.6 (1.03)	0.6 (0.85)	0.6 (0.87)
Visit 13/ET						
n/N1	45/59	21/29	36/59	16/31	81/118	37/60
Mean (SD)	0.6 (1.13)	0.6 (0.78)	0.6 (0.75)	0.6 (0.74)	0.6 (0.98)	0.6 (0.75)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.10)	0.1 (0.15)	-0.1 (0.11)	-0.1 (0.17)	0.0 (0.08)	-0.0 (0.12)
95% CI	[-0.16, 0.24]	[-0.22, 0.37]	[-0.28, 0.17]	[-0.41, 0.28]	[-0.16, 0.16]	[-0.24, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.01		0.01	
95% CI	[-0.39, 0.32]		[-0.40, 0.42]		[-0.28, 0.29]	
p-value	0.8417		0.9659		0.9652	
Hedges' g	-0.05		0.06		-0.00	
95% CI	[-0.57, 0.46]		[-0.54, 0.66]		[-0.39, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_15_1_1_m_ua_sex_pp.sas using SAS 9.4

Table 12.4.15.1.1.s2.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	47/56	32/33	51/60	26/29	98/116	58/62
Mean (SD)	0.7 (0.74)	0.7 (1.10)	0.8 (1.03)	0.9 (1.36)	0.7 (0.90)	0.8 (1.21)
Visit 13/ET						
n/N2	48/56	33/33	50/60	23/29	98/116	56/62
Mean (SD)	0.8 (0.92)	0.7 (0.96)	1.0 (1.20)	0.6 (0.76)	0.9 (1.08)	0.7 (0.87)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.09)	-0.0 (0.11)	0.2 (0.10)	-0.0 (0.14)	0.2 (0.07)	-0.0 (0.09)
95% CI	[-0.09, 0.28]	[-0.25, 0.19]	[0.02, 0.41]	[-0.31, 0.25]	[0.02, 0.29]	[-0.21, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.24		0.18	
95% CI	[-0.17, 0.41]		[-0.10, 0.58]		[-0.04, 0.40]	
p-value	0.4068		0.1660		0.1000	
Hedges' g	0.19		0.32		0.26	
95% CI	[-0.25, 0.63]		[-0.17, 0.81]		[-0.07, 0.59]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_15_1_1_m_ua_sex_pp.sas using SAS 9.4

Table 12.4.12.1.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4463		0.1320		0.6011	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	9.1 (0.26)	9.3 (0.26)	9.2 (0.30)	9.3 (0.23)	9.2 (0.29)	9.3 (0.24)
Visit 13/ET						
n/N1	58/58	29/30	60/60	24/24	118/118	53/54
Mean (SD)	9.4 (0.43)	9.3 (0.32)	9.5 (0.36)	9.5 (0.56)	9.5 (0.40)	9.4 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.08)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.18, 0.37]	[-0.05, 0.22]	[0.19, 0.38]	[0.04, 0.34]	[0.22, 0.35]	[0.04, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.10		0.14	
95% CI	[0.02, 0.35]		[-0.08, 0.27]		[0.02, 0.26]	
p-value	0.0284		0.2832		0.0186	
Hedges' g	0.60		0.27		0.45	
95% CI	[0.15, 1.05]		[-0.20, 0.74]		[0.13, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_1_m_dca_wt_pp.sas using SAS 9.4

Table 12.4.12.1.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	9.2 (0.28)	9.2 (0.29)	9.2 (0.33)	9.2 (0.30)	9.2 (0.31)	9.2 (0.30)
Visit 13/ET						
n/N2	57/57	32/32	57/59	33/36	114/116	65/68
Mean (SD)	9.5 (0.36)	9.4 (0.34)	9.5 (0.39)	9.3 (0.53)	9.5 (0.38)	9.3 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.3 (0.05)	0.0 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.18, 0.34]	[0.03, 0.25]	[0.22, 0.41]	[-0.08, 0.17]	[0.23, 0.35]	[0.01, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.27		0.19	
95% CI	[-0.01, 0.26]		[0.12, 0.42]		[0.09, 0.30]	
p-value	0.0784		0.0007		0.0002	
Hedges' g	0.36		0.76		0.57	
95% CI	[-0.07, 0.79]		[0.33, 1.20]		[0.26, 0.88]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_1_m_dca_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3628		0.9531		0.5374	
Comparison Baseline vs. EAP	0.1198		0.6030		0.1844	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	3.8 (0.59)	3.8 (0.63)	3.9 (0.58)	3.6 (0.38)	3.8 (0.58)	3.7 (0.54)
Visit 13/ET						
n/N1	58/58	29/30	60/60	24/24	118/118	53/54
Mean (SD)	4.0 (0.79)	3.9 (0.58)	4.0 (0.64)	3.6 (0.65)	4.0 (0.72)	3.8 (0.63)
EAP						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	4.0 (0.70)	4.0 (0.53)	4.1 (0.63)	3.6 (0.53)	4.0 (0.66)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.08)	0.1 (0.11)	0.2 (0.07)	-0.1 (0.12)	0.2 (0.05)	0.0 (0.08)
95% CI	[0.11, 0.42]	[-0.13, 0.31]	[0.05, 0.34]	[-0.32, 0.14]	[0.12, 0.33]	[-0.15, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.28		0.22	
95% CI	[-0.09, 0.44]		[0.01, 0.56]		[0.03, 0.41]	
p-value	0.1989		0.0431		0.0225	
Hedges' g	0.31		0.31		0.30	
95% CI	[-0.13, 0.76]		[-0.17, 0.78]		[-0.02, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.08)	0.2 (0.06)	-0.1 (0.10)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.15, 0.37]	[-0.01, 0.29]	[0.09, 0.33]	[-0.24, 0.14]	[0.15, 0.31]	[-0.07, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.26		0.18	
95% CI	[-0.07, 0.30]		[0.03, 0.49]		[0.03, 0.32]	
p-value	0.2158		0.0274		0.0155	
Hedges' g	0.31		0.39		0.33	
95% CI	[-0.13, 0.75]		[-0.09, 0.86]		[0.01, 0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	3.7 (0.49)	3.8 (0.56)	3.7 (0.56)	3.6 (0.48)	3.7 (0.52)	3.7 (0.52)
Visit 13/ET						
n/N2	57/57	32/32	57/59	33/36	114/116	65/68
Mean (SD)	3.8 (0.58)	3.8 (0.71)	4.0 (0.81)	3.8 (0.77)	3.9 (0.72)	3.8 (0.74)
EAP						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	3.7 (0.49)	3.9 (0.61)	4.0 (0.71)	3.8 (0.52)	3.9 (0.62)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.1 (0.10)	0.3 (0.09)	0.1 (0.11)	0.2 (0.06)	0.1 (0.07)
95% CI	[-0.08, 0.20]	[-0.12, 0.26]	[0.15, 0.49]	[-0.09, 0.36]	[0.09, 0.31]	[-0.05, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.19		0.10	
95% CI	[-0.25, 0.23]		[-0.09, 0.47]		[-0.09, 0.28]	
p-value	0.9336		0.1817		0.3030	
Hedges' g	0.03		0.29		0.16	
95% CI	[-0.40, 0.45]		[-0.14, 0.71]		[-0.14, 0.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.0 (0.05)	0.1 (0.07)	0.3 (0.06)	0.2 (0.08)	0.2 (0.04)	0.2 (0.05)
95% CI	[-0.07, 0.13]	[-0.01, 0.26]	[0.17, 0.42]	[0.03, 0.34]	[0.08, 0.24]	[0.05, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.09		0.11		0.01	
95% CI	[-0.26, 0.08]		[-0.09, 0.31]		[-0.12, 0.14]	
p-value	0.2754		0.2606		0.8440	
Hedges' g	-0.18		0.22		0.03	
95% CI	[-0.61, 0.25]		[-0.19, 0.63]		[-0.26, 0.33]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.5.1.1.1.s3.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1640		0.7157		0.5569	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	36/58	16/30	32/60	18/24	68/118	34/54
Mean (SD)	36.7 (24.08)	39.5 (38.09)	36.2 (30.08)	33.8 (28.97)	36.4 (26.87)	36.5 (33.17)
Visit 13/ET						
n/N1	35/58	7/30	36/60	8/24	71/118	15/54
Mean (SD)	51.5 (60.45)	38.2 (30.86)	56.6 (56.38)	74.3 (67.56)	54.0 (58.06)	57.5 (55.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	21.1 (11.36)	-12.9 (28.38)	26.1 (14.11)	36.7 (25.79)	23.5 (8.91)	13.2 (19.03)
95% CI	[-2.06, 44.30]	[-70.81, 44.94]	[-2.85, 55.04]	[-16.20, 89.64]	[5.68, 41.33]	[-24.90, 51.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	34.06		-10.62		10.33	
95% CI	[-29.06, 97.17]		[-71.28, 50.04]		[-32.05, 52.71]	
p-value	0.2796		0.7222		0.6274	
Hedges' g	0.67		-0.01		0.24	
95% CI	[-0.27, 1.61]		[-0.84, 0.81]		[-0.38, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_5_1_1_1_m_fgf23_wt_pp.sas using SAS 9.4

Table 12.5.1.1.1.s3.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	44/57	19/32	37/59	21/36	81/116	40/68
Mean (SD)	56.1 (68.07)	45.8 (33.80)	32.9 (20.52)	34.4 (23.47)	45.5 (53.05)	39.8 (29.04)
Visit 13/ET						
n/N2	34/57	15/32	31/59	17/36	65/116	32/68
Mean (SD)	45.4 (28.62)	44.2 (32.56)	67.1 (85.14)	58.1 (54.92)	55.7 (62.77)	51.6 (45.66)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-8.2 (5.25)	-9.2 (7.67)	42.2 (16.56)	23.7 (22.16)	16.3 (7.92)	6.3 (11.04)
95% CI	[-18.79, 2.36]	[-24.63, 6.30]	[8.59, 75.74]	[-21.27, 68.60]	[0.53, 32.03]	[-15.64, 28.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.95		18.50		9.95	
95% CI	[-17.81, 19.71]		[-37.73, 74.73]		[-17.11, 37.00]	
p-value	0.9190		0.5089		0.4666	
Hedges' g	-0.12		0.18		0.01	
95% CI	[-0.73, 0.48]		[-0.46, 0.82]		[-0.43, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_5_1_1_1_m_fgf23_wt_pp.sas using SAS 9.4

Table 12.4.12.1.2.s3.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4788		0.2410		0.1943	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	30.2 (10.62)	33.3 (11.95)	29.7 (8.82)	30.5 (8.41)	29.9 (9.70)	32.1 (10.54)
Visit 13/ET						
n/N1	58/58	29/30	60/60	24/24	118/118	53/54
Mean (SD)	28.9 (10.89)	33.0 (11.93)	27.6 (8.90)	29.5 (9.20)	28.2 (9.91)	31.4 (10.82)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.5 (0.81)	-0.5 (1.15)	-2.2 (0.61)	-0.9 (0.97)	-1.8 (0.51)	-0.7 (0.76)
95% CI	[-3.06, 0.16]	[-2.76, 1.80]	[-3.38, -0.94]	[-2.78, 1.08]	[-2.80, -0.81]	[-2.17, 0.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.97		-1.31		-1.13	
95% CI	[-3.78, 1.83]		[-3.60, 0.98]		[-2.94, 0.67]	
p-value	0.4920		0.2580		0.2174	
Hedges' g	-0.07		-0.25		-0.15	
95% CI	[-0.51, 0.37]		[-0.72, 0.22]		[-0.47, 0.17]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_2_m_egfr_wt_pp.sas using SAS 9.4

Table 12.4.12.1.2.s3.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	30.4 (11.45)	33.3 (10.32)	31.9 (10.02)	33.8 (9.64)	31.2 (10.72)	33.6 (9.89)
Visit 13/ET						
n/N2	57/57	32/32	57/59	33/36	114/116	65/68
Mean (SD)	31.1 (12.66)	32.7 (11.14)	30.8 (13.14)	31.8 (11.61)	31.0 (12.84)	32.3 (11.30)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.5 (1.08)	-0.3 (1.44)	-0.5 (0.93)	-1.6 (1.22)	0.0 (0.72)	-0.9 (0.96)
95% CI	[-1.65, 2.64]	[-3.13, 2.61]	[-2.36, 1.34]	[-4.01, 0.85]	[-1.42, 1.43]	[-2.82, 0.95]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.76		1.07		0.94	
95% CI	[-2.84, 4.36]		[-1.99, 4.14]		[-1.44, 3.31]	
p-value	0.6764		0.4879		0.4366	
Hedges' g	0.15		0.13		0.14	
95% CI	[-0.28, 0.58]		[-0.29, 0.56]		[-0.16, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_2_m_egfr_wt_pp.sas using SAS 9.4

Table 12.4.15.1.1.s3.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8871		0.0574		0.2031	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	49/58	26/30	44/60	19/24	93/118	45/54
Mean (SD)	0.6 (0.75)	0.6 (0.74)	0.7 (0.90)	0.6 (0.87)	0.6 (0.82)	0.6 (0.79)
Visit 13/ET						
n/N1	50/58	27/30	43/60	19/24	93/118	46/54
Mean (SD)	0.7 (1.17)	0.6 (0.88)	0.7 (0.87)	0.7 (0.81)	0.7 (1.04)	0.6 (0.84)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.09)	0.1 (0.13)	0.0 (0.10)	0.1 (0.14)	0.1 (0.07)	0.1 (0.10)
95% CI	[-0.06, 0.31]	[-0.18, 0.33]	[-0.15, 0.23]	[-0.14, 0.42]	[-0.06, 0.22]	[-0.09, 0.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		-0.10		-0.03	
95% CI	[-0.27, 0.37]		[-0.44, 0.24]		[-0.27, 0.21]	
p-value	0.7491		0.5731		0.8116	
Hedges' g	0.10		-0.22		-0.04	
95% CI	[-0.36, 0.56]		[-0.76, 0.32]		[-0.39, 0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_15_1_1_m_ua_wt_pp.sas using SAS 9.4

Table 12.4.15.1.1.s3.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	44/57	27/32	45/59	27/36	89/116	54/68
Mean (SD)	0.7 (0.83)	0.8 (1.13)	0.8 (1.02)	0.9 (1.43)	0.7 (0.93)	0.9 (1.28)
Visit 13/ET						
n/N2	43/57	27/32	43/59	20/36	86/116	47/68
Mean (SD)	0.7 (0.84)	0.7 (0.90)	0.9 (1.21)	0.5 (0.69)	0.8 (1.04)	0.7 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.09)	-0.0 (0.11)	0.2 (0.12)	-0.3 (0.18)	0.1 (0.07)	-0.1 (0.10)
95% CI	[-0.19, 0.16]	[-0.24, 0.20]	[-0.07, 0.42]	[-0.62, 0.11]	[-0.07, 0.23]	[-0.34, 0.07]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.00		0.43		0.22	
95% CI	[-0.28, 0.29]		[-0.01, 0.87]		[-0.03, 0.47]	
p-value	0.9760		0.0536		0.0886	
Hedges' g	0.05		0.52		0.29	
95% CI	[-0.43, 0.53]		[-0.02, 1.07]		[-0.07, 0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_15_1_1_m_ua_wt_pp.sas using SAS 9.4

Table 12.4.12.1.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5301		0.0034		0.0124	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	9.2 (0.26)	9.2 (0.29)	9.2 (0.32)	9.2 (0.28)	9.2 (0.29)	9.2 (0.29)
Visit 13/ET						
n/N1	65/65	41/41	82/83	39/39	147/148	80/80
Mean (SD)	9.4 (0.40)	9.3 (0.36)	9.6 (0.36)	9.3 (0.52)	9.5 (0.38)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.3 (0.04)	0.0 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.20, 0.36]	[0.00, 0.21]	[0.26, 0.41]	[-0.08, 0.14]	[0.25, 0.36]	[-0.01, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.31		0.24	
95% CI	[0.05, 0.31]		[0.18, 0.44]		[0.15, 0.34]	
p-value	0.0082		<0.0001		<0.0001	
Hedges' g	0.57		0.87		0.73	
95% CI	[0.17, 0.96]		[0.47, 1.26]		[0.45, 1.01]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_1_m_dca_race_pp.sas using SAS 9.4

Table 12.4.12.1.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	9.2 (0.29)	9.3 (0.24)	9.2 (0.32)	9.3 (0.26)	9.2 (0.30)	9.3 (0.25)
Visit 13/ET						
n/N2	50/50	20/21	35/36	18/21	85/86	38/42
Mean (SD)	9.5 (0.41)	9.4 (0.23)	9.5 (0.41)	9.5 (0.58)	9.5 (0.41)	9.5 (0.43)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.08)	0.2 (0.06)	0.3 (0.08)	0.2 (0.04)	0.2 (0.06)
95% CI	[0.15, 0.34]	[-0.01, 0.30]	[0.10, 0.34]	[0.11, 0.44]	[0.15, 0.31]	[0.09, 0.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.05		0.03	
95% CI	[-0.08, 0.28]		[-0.26, 0.15]		[-0.11, 0.17]	
p-value	0.2773		0.5937		0.6942	
Hedges' g	0.36		-0.16		0.13	
95% CI	[-0.16, 0.88]		[-0.72, 0.40]		[-0.25, 0.51]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_1_m_dca_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9840		0.0826		0.1850	
Comparison Baseline vs. EAP	0.9950		0.1392		0.2283	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	3.7 (0.57)	3.8 (0.60)	3.8 (0.56)	3.6 (0.39)	3.7 (0.56)	3.7 (0.51)
Visit 13/ET						
n/N1	65/65	41/41	82/83	39/39	147/148	80/80
Mean (SD)	3.9 (0.71)	3.9 (0.69)	4.0 (0.74)	3.6 (0.67)	4.0 (0.73)	3.8 (0.69)
EAP						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	3.9 (0.63)	3.9 (0.61)	4.0 (0.68)	3.7 (0.50)	3.9 (0.66)	3.8 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.09)	0.3 (0.07)	-0.0 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.03, 0.32]	[-0.09, 0.28]	[0.14, 0.40]	[-0.23, 0.15]	[0.13, 0.32]	[-0.11, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.31		0.20	
95% CI	[-0.15, 0.32]		[0.08, 0.55]		[0.04, 0.37]	
p-value	0.4913		0.0086		0.0143	
Hedges' g	0.18		0.47		0.33	
95% CI	[-0.21, 0.57]		[0.09, 0.85]		[0.06, 0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.3 (0.05)	0.0 (0.07)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.04, 0.25]	[0.00, 0.27]	[0.15, 0.35]	[-0.12, 0.17]	[0.13, 0.27]	[-0.02, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.23		0.12	
95% CI	[-0.16, 0.18]		[0.05, 0.40]		[0.00, 0.24]	
p-value	0.9078		0.0126		0.0499	
Hedges' g	0.07		0.45		0.27	
95% CI	[-0.32, 0.46]		[0.07, 0.83]		[-0.00, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	3.7 (0.50)	3.8 (0.59)	3.8 (0.60)	3.6 (0.54)	3.8 (0.55)	3.7 (0.56)
Visit 13/ET						
n/N2	50/50	20/21	35/36	18/21	85/86	38/42
Mean (SD)	3.9 (0.71)	3.8 (0.56)	4.0 (0.69)	3.9 (0.80)	3.9 (0.70)	3.9 (0.68)
EAP						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	3.9 (0.61)	3.9 (0.50)	4.1 (0.65)	3.9 (0.57)	3.9 (0.63)	3.9 (0.53)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.1 (0.12)	0.2 (0.10)	0.2 (0.15)	0.2 (0.06)	0.2 (0.09)
95% CI	[0.00, 0.31]	[-0.18, 0.30]	[0.01, 0.43]	[-0.05, 0.54]	[0.06, 0.31]	[-0.03, 0.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.02		0.03	
95% CI	[-0.19, 0.38]		[-0.39, 0.34]		[-0.19, 0.26]	
p-value	0.5066		0.8924		0.7806	
Hedges' g	0.18		-0.13		0.01	
95% CI	[-0.34, 0.69]		[-0.69, 0.43]		[-0.37, 0.39]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.08)	0.2 (0.08)	0.2 (0.11)	0.2 (0.05)	0.2 (0.07)
95% CI	[0.04, 0.25]	[-0.04, 0.29]	[0.08, 0.42]	[-0.02, 0.42]	[0.10, 0.29]	[0.04, 0.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.05		0.02	
95% CI	[-0.18, 0.22]		[-0.23, 0.33]		[-0.14, 0.19]	
p-value	0.8463		0.7234		0.7903	
Hedges' g	0.07		-0.05		-0.01	
95% CI	[-0.43, 0.57]		[-0.58, 0.49]		[-0.38, 0.36]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.5.1.1.1.s4.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6076		0.7033		0.8725	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	46/65	21/41	44/83	24/39	90/148	45/80
Mean (SD)	54.8 (66.49)	49.0 (38.13)	34.2 (26.89)	32.2 (22.98)	44.7 (51.89)	40.1 (31.76)
Visit 13/ET						
n/N1	39/65	16/41	47/83	11/39	86/148	27/80
Mean (SD)	52.7 (54.02)	41.6 (30.84)	60.5 (71.12)	61.5 (72.59)	57.0 (63.70)	49.7 (51.71)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	1.5 (8.31)	-11.9 (13.34)	33.0 (13.99)	28.3 (25.45)	16.8 (7.89)	7.4 (13.57)
95% CI	[-15.23, 18.22]	[-38.74, 14.94]	[4.71, 61.27]	[-23.15, 79.72]	[1.11, 32.47]	[-19.62, 34.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	13.40		4.70		9.44	
95% CI	[-18.24, 45.04]		[-54.05, 63.45]		[-21.76, 40.64]	
p-value	0.3987		0.8723		0.5493	
Hedges' g	0.10		0.02		0.09	
95% CI	[-0.51, 0.71]		[-0.67, 0.72]		[-0.37, 0.55]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_5_1_1_1_m_fgf23_race_pp.sas using SAS 9.4

Table 12.5.1.1.1.s4.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	34/50	14/21	25/36	15/21	59/86	29/42
Mean (SD)	37.2 (25.84)	33.8 (29.91)	34.9 (22.64)	37.1 (30.39)	36.2 (24.36)	35.5 (29.66)
Visit 13/ET						
n/N2	30/50	6/21	20/36	14/21	50/86	20/42
Mean (SD)	43.0 (36.88)	44.1 (35.89)	63.6 (71.72)	64.7 (47.14)	51.2 (53.89)	58.5 (44.20)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.9 (7.87)	6.3 (16.40)	37.6 (18.20)	28.0 (21.30)	23.2 (9.00)	16.9 (14.14)
95% CI	[-7.22, 25.04]	[-27.34, 39.86]	[-0.09, 75.19]	[-16.06, 72.05]	[5.19, 41.29]	[-11.52, 45.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	2.65		9.56		6.39	
95% CI	[-35.00, 40.30]		[-48.79, 67.90]		[-27.55, 40.33]	
p-value	0.8865		0.7378		0.7072	
Hedges' g	0.38		0.22		0.15	
95% CI	[-0.49, 1.25]		[-0.53, 0.98]		[-0.41, 0.71]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_5_1_1_1_m_fgf23_race_pp.sas using SAS 9.4

Table 12.4.12.1.2.s4.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0364		0.0047		0.0005	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	28.5 (9.49)	32.3 (11.08)	30.2 (9.12)	30.4 (8.28)	29.5 (9.29)	31.4 (9.80)
Visit 13/ET						
n/N1	65/65	41/41	82/83	39/39	147/148	80/80
Mean (SD)	27.3 (9.45)	32.7 (12.14)	27.8 (9.67)	30.3 (10.86)	27.6 (9.54)	31.5 (11.53)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.4 (0.78)	0.8 (0.98)	-2.2 (0.53)	-0.1 (0.77)	-1.8 (0.46)	0.3 (0.62)
95% CI	[-2.96, 0.13]	[-1.17, 2.74]	[-3.29, -1.19]	[-1.63, 1.42]	[-2.69, -0.87]	[-0.97, 1.49]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-2.20		-2.14		-2.04	
95% CI	[-4.71, 0.31]		[-3.99, -0.29]		[-3.57, -0.50]	
p-value	0.0853		0.0237		0.0094	
Hedges' g	-0.25		-0.45		-0.35	
95% CI	[-0.64, 0.14]		[-0.83, -0.06]		[-0.62, -0.07]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_2_m_egfr_race_pp.sas using SAS 9.4

Table 12.4.12.1.2.s4.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	32.7 (12.37)	35.3 (10.99)	32.1 (10.21)	36.4 (9.85)	32.4 (11.45)	35.9 (10.32)
Visit 13/ET						
n/N2	50/50	20/21	35/36	18/21	85/86	38/42
Mean (SD)	33.5 (13.59)	33.1 (10.10)	32.2 (13.95)	32.2 (10.30)	33.0 (13.67)	32.7 (10.07)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.7 (1.18)	-2.5 (1.87)	0.7 (1.37)	-3.7 (1.92)	0.6 (0.91)	-3.0 (1.35)
95% CI	[-1.69, 3.01]	[-6.28, 1.19]	[-2.05, 3.45]	[-7.61, 0.12]	[-1.20, 2.41]	[-5.72, -0.37]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.20		4.45		3.66	
95% CI	[-1.23, 7.63]		[-0.34, 9.24]		[0.41, 6.90]	
p-value	0.1536		0.0681		0.0275	
Hedges' g	0.44		0.55		0.50	
95% CI	[-0.07, 0.96]		[-0.02, 1.11]		[0.11, 0.88]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_2_m_egfr_race_pp.sas using SAS 9.4

Table 12.4.15.1.1.s4.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7945		0.5692		0.8207	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	50/65	36/41	62/83	30/39	112/148	66/80
Mean (SD)	0.6 (0.83)	0.7 (0.91)	0.7 (0.97)	0.7 (1.11)	0.7 (0.91)	0.7 (1.00)
Visit 13/ET						
n/N1	51/65	39/41	59/83	26/39	110/148	65/80
Mean (SD)	0.6 (0.87)	0.6 (0.85)	0.8 (1.11)	0.7 (0.78)	0.7 (1.01)	0.6 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.08)	-0.0 (0.10)	0.1 (0.09)	-0.1 (0.13)	0.1 (0.06)	-0.0 (0.08)
95% CI	[-0.18, 0.15]	[-0.21, 0.18]	[-0.06, 0.29]	[-0.34, 0.19]	[-0.07, 0.17]	[-0.21, 0.11]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		0.19		0.10	
95% CI	[-0.26, 0.25]		[-0.12, 0.51]		[-0.10, 0.30]	
p-value	0.9949		0.2294		0.3425	
Hedges' g	0.01		0.28		0.15	
95% CI	[-0.41, 0.42]		[-0.18, 0.75]		[-0.16, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_15_1_1_m_ua_race_pp.sas using SAS 9.4

Table 12.4.15.1.1.s4.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	43/50	17/21	27/36	16/21	70/86	33/42
Mean (SD)	0.6 (0.75)	0.7 (1.08)	0.8 (0.95)	1.0 (1.44)	0.7 (0.83)	0.8 (1.25)
Visit 13/ET						
n/N2	42/50	15/21	27/36	13/21	69/86	28/42
Mean (SD)	0.8 (1.18)	0.7 (1.00)	0.8 (0.95)	0.5 (0.69)	0.8 (1.09)	0.7 (0.86)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.11)	0.1 (0.18)	0.1 (0.15)	-0.1 (0.22)	0.1 (0.10)	0.0 (0.15)
95% CI	[-0.05, 0.38]	[-0.27, 0.46]	[-0.20, 0.43]	[-0.50, 0.39]	[-0.06, 0.32]	[-0.25, 0.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.07		0.17		0.08	
95% CI	[-0.35, 0.50]		[-0.38, 0.72]		[-0.27, 0.43]	
p-value	0.7329		0.5328		0.6415	
Hedges' g	0.10		0.05		0.09	
95% CI	[-0.48, 0.69]		[-0.60, 0.70]		[-0.35, 0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_15_1_1_m_ua_race_pp.sas using SAS 9.4

Table 12.4.12.1.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2737		0.0378		0.5085	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	9.2 (0.28)	9.3 (0.26)	9.3 (0.33)	9.3 (0.25)	9.2 (0.30)	9.3 (0.26)
Visit 13/ET						
n/N1	58/58	33/33	63/65	26/29	121/123	59/62
Mean (SD)	9.5 (0.41)	9.3 (0.29)	9.5 (0.37)	9.5 (0.50)	9.5 (0.39)	9.4 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.04)	0.2 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.18, 0.36]	[-0.05, 0.19]	[0.20, 0.36]	[0.11, 0.35]	[0.21, 0.33]	[0.06, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.05		0.13	
95% CI	[0.05, 0.35]		[-0.10, 0.19]		[0.02, 0.23]	
p-value	0.0087		0.5333		0.0161	
Hedges' g	0.64		0.15		0.44	
95% CI	[0.20, 1.07]		[-0.30, 0.60]		[0.12, 0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_1_m_dca_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	9.1 (0.27)	9.2 (0.28)	9.2 (0.30)	9.2 (0.30)	9.2 (0.29)	9.2 (0.29)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	9.4 (0.39)	9.3 (0.37)	9.5 (0.38)	9.2 (0.57)	9.5 (0.39)	9.3 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.2 (0.06)	0.3 (0.05)	0.0 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.18, 0.35]	[0.05, 0.30]	[0.22, 0.44]	[-0.14, 0.14]	[0.23, 0.36]	[-0.00, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.33		0.21	
95% CI	[-0.06, 0.24]		[0.15, 0.50]		[0.09, 0.32]	
p-value	0.2360		0.0004		0.0004	
Hedges' g	0.29		0.83		0.59	
95% CI	[-0.16, 0.74]		[0.38, 1.29]		[0.27, 0.91]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_1_m_dca_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2405		0.7860		0.2967	
Comparison Baseline vs. EAP	0.9006		0.2885		0.3629	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	3.5 (0.49)	3.7 (0.57)	3.6 (0.54)	3.5 (0.42)	3.6 (0.52)	3.6 (0.50)
Visit 13/ET						
n/N1	58/58	33/33	63/65	26/29	121/123	59/62
Mean (SD)	3.6 (0.60)	3.8 (0.61)	3.7 (0.59)	3.6 (0.70)	3.7 (0.60)	3.7 (0.66)
EAP						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	3.6 (0.51)	3.8 (0.54)	3.7 (0.46)	3.6 (0.47)	3.7 (0.49)	3.7 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.2 (0.09)	0.1 (0.06)	-0.0 (0.10)	0.1 (0.05)	0.1 (0.07)
95% CI	[-0.03, 0.23]	[-0.01, 0.34]	[0.00, 0.26]	[-0.22, 0.18]	[0.03, 0.21]	[-0.06, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.07		0.15		0.05	
95% CI	[-0.29, 0.15]		[-0.08, 0.39]		[-0.11, 0.20]	
p-value	0.5457		0.1996		0.5781	
Hedges' g	-0.02		0.25		0.10	
95% CI	[-0.44, 0.41]		[-0.20, 0.71]		[-0.21, 0.41]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.1 (0.04)	0.1 (0.06)	0.1 (0.03)	0.1 (0.05)
95% CI	[0.01, 0.21]	[0.01, 0.28]	[0.04, 0.20]	[-0.07, 0.18]	[0.05, 0.18]	[0.01, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.06		0.01	
95% CI	[-0.20, 0.14]		[-0.09, 0.21]		[-0.10, 0.12]	
p-value	0.7073		0.4009		0.8333	
Hedges' g	0.05		0.10		0.07	
95% CI	[-0.38, 0.47]		[-0.33, 0.53]		[-0.24, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	3.9 (0.51)	3.9 (0.60)	4.0 (0.54)	3.7 (0.45)	4.0 (0.53)	3.8 (0.54)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	4.2 (0.72)	3.9 (0.70)	4.4 (0.73)	3.9 (0.72)	4.3 (0.73)	3.9 (0.71)
EAP						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	4.1 (0.64)	4.1 (0.58)	4.4 (0.71)	3.9 (0.57)	4.2 (0.68)	4.0 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	-0.0 (0.12)	0.4 (0.09)	0.1 (0.12)	0.3 (0.06)	0.0 (0.08)
95% CI	[0.06, 0.39]	[-0.25, 0.22]	[0.23, 0.60]	[-0.17, 0.32]	[0.20, 0.44]	[-0.14, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.24		0.34		0.29	
95% CI	[-0.05, 0.53]		[0.03, 0.65]		[0.08, 0.50]	
p-value	0.0971		0.0302		0.0060	
Hedges' g	0.35		0.34		0.34	
95% CI	[-0.10, 0.80]		[-0.10, 0.78]		[0.02, 0.66]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.4 (0.07)	0.1 (0.10)	0.3 (0.05)	0.1 (0.06)
95% CI	[0.06, 0.29]	[-0.03, 0.29]	[0.27, 0.57]	[-0.10, 0.30]	[0.20, 0.39]	[-0.00, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.32		0.17	
95% CI	[-0.16, 0.24]		[0.06, 0.57]		[0.02, 0.33]	
p-value	0.6966		0.0144		0.0314	
Hedges' g	0.09		0.44		0.27	
95% CI	[-0.36, 0.53]		[-0.01, 0.88]		[-0.04, 0.59]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s5.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4808		0.1544		0.1539	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	33/58	14/33	33/65	17/29	66/123	31/62
Mean (SD)	43.8 (32.59)	42.1 (40.04)	34.9 (30.28)	30.7 (20.06)	39.3 (31.54)	35.8 (30.71)
Visit 13/ET						
n/N1	29/58	10/33	28/65	9/29	57/123	19/62
Mean (SD)	32.3 (22.64)	38.9 (32.80)	36.3 (20.77)	62.2 (46.65)	34.3 (21.64)	49.9 (40.58)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-6.3 (5.42)	-3.0 (8.99)	-1.9 (7.41)	19.6 (11.88)	-4.2 (4.58)	8.4 (7.45)
95% CI	[-17.44, 4.80]	[-21.41, 15.49]	[-17.28, 13.45]	[-5.02, 44.27]	[-13.35, 5.04]	[-6.54, 23.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-3.36		-21.54		-12.59	
95% CI	[-24.90, 18.18]		[-50.59, 7.50]		[-30.16, 4.98]	
p-value	0.7514		0.1383		0.1562	
Hedges' g	-0.10		-0.45		-0.30	
95% CI	[-0.89, 0.69]		[-1.31, 0.40]		[-0.89, 0.28]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_5_1_1_1_m_fgf23_ckd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s5.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	47/57	21/29	36/54	22/31	83/111	43/60
Mean (SD)	49.8 (64.66)	43.5 (33.02)	34.0 (20.03)	36.8 (29.68)	43.0 (50.78)	40.0 (31.16)
Visit 13/ET						
n/N2	40/57	12/29	39/54	16/31	79/111	28/60
Mean (SD)	60.1 (56.52)	45.1 (31.40)	79.5 (87.13)	63.9 (65.44)	69.7 (73.42)	55.8 (53.58)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	9.9 (8.43)	-6.4 (15.20)	57.2 (15.60)	30.2 (22.86)	32.7 (8.59)	12.3 (13.91)
95% CI	[-7.03, 26.88]	[-36.98, 24.16]	[25.73, 88.74]	[-15.98, 76.35]	[15.63, 49.75]	[-15.39, 39.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	16.33		27.05		20.44	
95% CI	[-18.63, 51.30]		[-28.91, 83.01]		[-12.06, 52.94]	
p-value	0.3523		0.3347		0.2147	
Hedges' g	0.27		0.32		0.23	
95% CI	[-0.37, 0.91]		[-0.31, 0.94]		[-0.22, 0.68]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_5_1_1_1_m_fgf23_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s5.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7676		0.9941		0.8592	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	38.2 (9.31)	40.5 (9.63)	37.3 (7.34)	39.4 (7.72)	37.7 (8.30)	40.0 (8.73)
Visit 13/ET						
n/N1	58/58	33/33	63/65	26/29	121/123	59/62
Mean (SD)	37.6 (9.74)	39.2 (9.73)	36.4 (9.93)	39.2 (8.15)	37.0 (9.82)	39.2 (8.99)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.8 (0.96)	-0.8 (1.28)	-0.7 (0.90)	-0.0 (1.41)	-0.8 (0.66)	-0.4 (0.95)
95% CI	[-2.76, 1.07]	[-3.39, 1.70]	[-2.52, 1.06]	[-2.83, 2.77]	[-2.10, 0.50]	[-2.28, 1.48]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		-0.70		-0.40	
95% CI	[-3.20, 3.19]		[-4.04, 2.64]		[-2.70, 1.89]	
p-value	0.9980		0.6787		0.7296	
Hedges' g	0.09		-0.04		0.03	
95% CI	[-0.33, 0.51]		[-0.50, 0.41]		[-0.28, 0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_2_m_egfr_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s5.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	22.3 (5.36)	25.2 (5.64)	22.9 (4.36)	26.0 (4.67)	22.6 (4.89)	25.6 (5.13)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	22.3 (8.20)	25.4 (8.51)	20.7 (5.11)	23.9 (6.83)	21.5 (6.89)	24.6 (7.64)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.2 (0.93)	0.3 (1.34)	-2.4 (0.63)	-1.7 (0.84)	-1.3 (0.56)	-0.7 (0.78)
95% CI	[-2.02, 1.68]	[-2.36, 2.98]	[-3.68, -1.20]	[-3.35, -0.02]	[-2.41, -0.19]	[-2.24, 0.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.48		-0.75		-0.61	
95% CI	[-3.77, 2.82]		[-2.88, 1.37]		[-2.54, 1.33]	
p-value	0.7733		0.4829		0.5362	
Hedges' g	-0.00		-0.05		-0.01	
95% CI	[-0.45, 0.45]		[-0.48, 0.39]		[-0.32, 0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_2_m_egfr_ckd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s5.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7505		0.3031		0.3654	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	42/58	26/33	43/65	17/29	85/123	43/62
Mean (SD)	0.5 (0.65)	0.4 (0.87)	0.6 (0.93)	0.8 (1.44)	0.5 (0.80)	0.6 (1.13)
Visit 13/ET						
n/N1	43/58	27/33	44/65	17/29	87/123	44/62
Mean (SD)	0.5 (0.77)	0.5 (0.99)	0.7 (0.99)	0.6 (0.77)	0.6 (0.89)	0.6 (0.90)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.10)	0.1 (0.11)	0.1 (0.18)	0.1 (0.07)	0.1 (0.10)
95% CI	[-0.08, 0.24]	[-0.13, 0.26]	[-0.09, 0.36]	[-0.21, 0.51]	[-0.03, 0.24]	[-0.08, 0.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		-0.01		-0.00	
95% CI	[-0.24, 0.26]		[-0.44, 0.41]		[-0.24, 0.23]	
p-value	0.9178		0.9573		0.9867	
Hedges' g	0.02		-0.04		0.00	
95% CI	[-0.46, 0.50]		[-0.61, 0.53]		[-0.36, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_15_1_1_m_ua_ckd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s5.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	51/57	27/29	46/54	29/31	97/111	56/60
Mean (SD)	0.8 (0.86)	0.9 (0.99)	0.8 (0.98)	0.8 (1.11)	0.8 (0.92)	0.9 (1.04)
Visit 13/ET						
n/N2	50/57	27/29	42/54	22/31	92/111	49/60
Mean (SD)	0.9 (1.19)	0.8 (0.75)	1.0 (1.11)	0.6 (0.74)	0.9 (1.15)	0.7 (0.74)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.11)	-0.0 (0.15)	0.1 (0.11)	-0.2 (0.15)	0.1 (0.08)	-0.1 (0.11)
95% CI	[-0.16, 0.28]	[-0.33, 0.26]	[-0.13, 0.30]	[-0.52, 0.09]	[-0.08, 0.22]	[-0.33, 0.09]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.30		0.19	
95% CI	[-0.27, 0.46]		[-0.07, 0.67]		[-0.07, 0.45]	
p-value	0.6134		0.1105		0.1440	
Hedges' g	0.13		0.36		0.23	
95% CI	[-0.33, 0.59]		[-0.16, 0.87]		[-0.11, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_15_1_1_m_ua_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4848		0.6576		0.3449	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	9.3 (0.25)	9.2 (0.27)	9.3 (0.28)	9.2 (0.31)	9.3 (0.27)	9.2 (0.28)
Visit 13/ET						
n/N1	36/36	23/23	46/48	16/16	82/84	39/39
Mean (SD)	9.5 (0.39)	9.3 (0.35)	9.6 (0.33)	9.4 (0.64)	9.6 (0.36)	9.4 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.08)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.10, 0.31]	[-0.04, 0.23]	[0.20, 0.39]	[0.02, 0.34]	[0.18, 0.32]	[0.03, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.12		0.12	
95% CI	[-0.06, 0.29]		[-0.07, 0.30]		[-0.01, 0.24]	
p-value	0.2009		0.2149		0.0688	
Hedges' g	0.31		0.37		0.38	
95% CI	[-0.21, 0.83]		[-0.20, 0.93]		[-0.00, 0.76]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_1_m_dca_ttlpth_pp.sas using SAS 9.4

Table 12.4.12.1.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	9.2 (0.26)	9.2 (0.30)	9.3 (0.38)	9.3 (0.23)	9.2 (0.32)	9.3 (0.27)
Visit 13/ET						
n/N2	42/42	22/22	37/37	22/23	79/79	44/45
Mean (SD)	9.4 (0.42)	9.3 (0.31)	9.5 (0.37)	9.4 (0.40)	9.4 (0.40)	9.3 (0.36)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.06)	0.1 (0.07)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.08, 0.29]	[-0.08, 0.21]	[0.13, 0.35]	[-0.05, 0.24]	[0.14, 0.29]	[-0.02, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.15		0.13	
95% CI	[-0.06, 0.30]		[-0.03, 0.33]		[0.00, 0.26]	
p-value	0.1993		0.1096		0.0419	
Hedges' g	0.38		0.45		0.42	
95% CI	[-0.13, 0.89]		[-0.08, 0.97]		[0.05, 0.79]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_1_m_dca_ttlpth_pp.sas using SAS 9.4

Table 12.4.12.1.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	9.1 (0.29)	9.2 (0.26)	9.1 (0.25)	9.2 (0.30)	9.1 (0.27)	9.2 (0.28)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	9.5 (0.39)	9.4 (0.32)	9.5 (0.43)	9.3 (0.64)	9.5 (0.41)	9.3 (0.51)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.05)	0.2 (0.08)	0.4 (0.07)	0.1 (0.09)	0.4 (0.04)	0.1 (0.06)
95% CI	[0.31, 0.53]		[0.23, 0.51]		[0.31, 0.48]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.21		0.32		0.27	
95% CI	[0.02, 0.41]		[0.08, 0.56]		[0.11, 0.42]	
p-value	0.0330		0.0102		0.0010	
Hedges' g	0.77		0.72		0.76	
95% CI	[0.17, 1.36]		[0.15, 1.29]		[0.35, 1.18]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_1_m_dca_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5097		0.7634		0.9365	
Comparison Baseline vs. EAP	0.0523		0.6627		0.5763	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	3.6 (0.50)	3.6 (0.55)	3.7 (0.52)	3.4 (0.46)	3.6 (0.51)	3.6 (0.52)
Visit 13/ET						
n/N1	36/36	23/23	46/48	16/16	82/84	39/39
Mean (SD)	3.7 (0.57)	3.8 (0.70)	3.9 (0.63)	3.5 (0.48)	3.8 (0.61)	3.7 (0.64)
EAP						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	3.7 (0.54)	3.9 (0.57)	3.9 (0.58)	3.6 (0.42)	3.8 (0.57)	3.7 (0.53)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.09)	0.2 (0.12)	0.3 (0.07)	-0.0 (0.12)	0.2 (0.06)	0.1 (0.08)
95% CI	[-0.05, 0.32]	[-0.06, 0.41]	[0.13, 0.41]	[-0.25, 0.24]	[0.09, 0.32]	[-0.09, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.28		0.13	
95% CI	[-0.34, 0.26]		[-0.01, 0.56]		[-0.07, 0.33]	
p-value	0.7940		0.0549		0.2097	
Hedges' g	-0.03		0.41		0.17	
95% CI	[-0.54, 0.49]		[-0.15, 0.98]		[-0.21, 0.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.2 (0.08)	0.3 (0.05)	0.1 (0.09)	0.2 (0.04)	0.2 (0.06)
95% CI	[-0.03, 0.24]	[0.05, 0.38]	[0.16, 0.37]	[-0.07, 0.30]	[0.10, 0.27]	[0.04, 0.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.11		0.15		0.02	
95% CI	[-0.32, 0.10]		[-0.06, 0.36]		[-0.12, 0.17]	
p-value	0.2967		0.1642		0.7543	
Hedges' g	-0.24		0.29		0.02	
95% CI	[-0.75, 0.28]		[-0.27, 0.85]		[-0.35, 0.40]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	3.7 (0.56)	3.9 (0.51)	3.8 (0.62)	3.8 (0.44)	3.7 (0.58)	3.8 (0.47)
Visit 13/ET						
n/N2	42/42	22/22	37/37	22/23	79/79	44/45
Mean (SD)	4.0 (0.72)	3.9 (0.67)	4.0 (0.73)	3.9 (0.91)	4.0 (0.72)	3.9 (0.79)
EAP						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	4.0 (0.58)	3.9 (0.56)	3.9 (0.59)	3.9 (0.64)	4.0 (0.58)	3.9 (0.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.0 (0.12)	0.2 (0.11)	0.1 (0.14)	0.2 (0.07)	0.1 (0.09)
95% CI	[0.04, 0.39]	[-0.23, 0.26]	[0.02, 0.45]	[-0.13, 0.43]	[0.09, 0.36]	[-0.10, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.09		0.15	
95% CI	[-0.10, 0.50]		[-0.27, 0.44]		[-0.08, 0.37]	
p-value	0.1832		0.6166		0.2021	
Hedges' g	0.40		0.13		0.26	
95% CI	[-0.11, 0.92]		[-0.39, 0.65]		[-0.11, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.0 (0.08)	0.2 (0.08)	0.1 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[0.14, 0.36]	[-0.11, 0.20]	[0.01, 0.31]	[-0.07, 0.32]	[0.11, 0.30]	[-0.04, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.04		0.12	
95% CI	[0.01, 0.40]		[-0.21, 0.28]		[-0.04, 0.27]	
p-value	0.0388		0.7709		0.1375	
Hedges' g	0.61		0.06		0.31	
95% CI	[0.09, 1.13]		[-0.46, 0.57]		[-0.06, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	3.8 (0.54)	3.9 (0.72)	4.0 (0.55)	3.7 (0.37)	3.9 (0.55)	3.8 (0.56)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	4.0 (0.79)	3.9 (0.56)	4.2 (0.82)	3.7 (0.60)	4.1 (0.81)	3.8 (0.59)
EAP						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	3.9 (0.71)	4.0 (0.60)	4.3 (0.80)	3.7 (0.46)	4.1 (0.77)	3.9 (0.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	0.0 (0.15)	0.3 (0.12)	-0.1 (0.16)	0.2 (0.08)	-0.0 (0.11)
95% CI	[-0.06, 0.34]		[0.03, 0.52]		[0.05, 0.36]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.34		0.21	
95% CI	[-0.27, 0.46]		[-0.07, 0.76]		[-0.06, 0.48]	
p-value	0.6009		0.1053		0.1246	
Hedges' g	0.16		0.31		0.24	
95% CI	[-0.41, 0.74]		[-0.25, 0.87]		[-0.16, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.11)	0.3 (0.10)	0.0 (0.13)	0.2 (0.06)	0.1 (0.09)
95% CI	[-0.09, 0.22]		[0.13, 0.55]		[0.07, 0.33]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.07		0.32		0.12	
95% CI	[-0.35, 0.21]		[-0.02, 0.67]		[-0.10, 0.33]	
p-value	0.6080		0.0661		0.2827	
Hedges' g	-0.12		0.39		0.16	
95% CI	[-0.69, 0.45]		[-0.15, 0.94]		[-0.23, 0.55]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.5.1.1.1.s6.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8679		0.9607		0.9934	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	15/36	9/23	22/48	6/16	37/84	15/39
Mean (SD)	43.3 (37.69)	46.7 (39.56)	35.4 (32.54)	28.8 (18.79)	38.6 (34.43)	39.5 (33.21)
Visit 13/ET						
n/N1	13/36	6/23	23/48	4/16	36/84	10/39
Mean (SD)	38.1 (28.36)	46.6 (28.85)	42.2 (27.77)	35.6 (23.79)	40.7 (27.65)	42.2 (26.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-4.5 (7.28)	-3.7 (10.80)	13.1 (6.81)	-2.9 (11.83)	4.0 (5.48)	-2.4 (8.81)
95% CI	[-20.28, 11.19]	[-27.01, 19.67]	[-1.62, 27.82]	[-28.42, 22.68]	[-7.27, 15.22]	[-20.50, 15.66]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.87		15.97		6.40	
95% CI	[-29.02, 27.28]		[-13.56, 45.50]		[-14.90, 27.70]	
p-value	0.9475		0.2637		0.5428	
Hedges' g	-0.02		0.16		0.12	
95% CI	[-1.02, 0.98]		[-0.91, 1.23]		[-0.63, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_5_1_1_1_m_fgf23_ttlpth_pp.sas using SAS 9.4

Table 12.5.1.1.1.s6.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	32/42	13/22	21/37	15/23	53/79	28/45
Mean (SD)	35.9 (19.37)	31.7 (34.34)	35.3 (23.85)	26.7 (18.36)	35.6 (21.04)	29.0 (26.56)
Visit 13/ET						
n/N2	27/42	7/22	24/37	9/23	51/79	16/45
Mean (SD)	40.3 (36.53)	40.3 (42.87)	69.6 (81.18)	69.4 (50.06)	54.1 (62.81)	56.7 (47.89)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.4 (7.97)	1.3 (15.86)	47.5 (21.18)	41.7 (35.85)	27.3 (10.15)	21.8 (18.34)
95% CI	[-8.97, 23.81]	[-31.33, 33.86]	[3.36, 91.71]	[-33.04, 116.53]	[6.86, 47.70]	[-15.10, 58.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	6.15		5.79		5.48	
95% CI	[-30.64, 42.95]		[-81.46, 93.05]		[-36.72, 47.67]	
p-value	0.7338		0.8913		0.7951	
Hedges' g	0.34		0.01		0.07	
95% CI	[-0.54, 1.22]		[-0.89, 0.91]		[-0.57, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_5_1_1_1_m_fgf23_ttlpth_pp.sas using SAS 9.4

Table 12.5.1.1.1.s6.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	33/37	13/17	26/34	18/21	59/71	31/38
Mean (SD)	60.3 (76.14)	51.5 (33.27)	33.0 (19.70)	42.1 (31.31)	48.2 (59.61)	46.0 (31.95)
Visit 13/ET						
n/N3	29/37	9/17	20/34	12/21	49/71	21/38
Mean (SD)	60.7 (59.76)	40.9 (25.95)	73.8 (88.51)	67.9 (71.51)	66.1 (72.29)	56.3 (57.17)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	6.3 (10.80)	-14.9 (18.72)	38.9 (19.54)	27.2 (25.85)	20.4 (10.61)	8.2 (15.92)
95% CI	[-15.63, 28.33]		[-1.22, 78.97]		[-0.85, 41.59]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	21.20		11.63		12.21	
95% CI	[-22.79, 65.19]		[-55.61, 78.86]		[-26.05, 50.47]	
p-value	0.3340		0.7255		0.5258	
Hedges' g	0.17		0.17		0.11	
95% CI	[-0.57, 0.90]		[-0.56, 0.89]		[-0.41, 0.63]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_5_1_1_1_m_fgf23_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5210		0.7370		0.8225	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	37.5 (12.32)	39.3 (12.19)	33.3 (9.88)	37.3 (9.24)	35.1 (11.12)	38.5 (10.99)
Visit 13/ET						
n/N1	36/36	23/23	46/48	16/16	82/84	39/39
Mean (SD)	36.0 (12.11)	38.3 (11.87)	32.3 (12.42)	36.3 (10.48)	33.9 (12.34)	37.5 (11.22)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.7 (1.23)	-0.7 (1.54)	-0.3 (1.01)	-1.1 (1.74)	-1.0 (0.80)	-0.7 (1.18)
95% CI	[-4.13, 0.81]	[-3.80, 2.38]	[-2.29, 1.77]	[-4.61, 2.35]	[-2.61, 0.58]	[-3.04, 1.65]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.95		0.87		-0.32	
95% CI	[-4.91, 3.01]		[-3.19, 4.94]		[-3.16, 2.53]	
p-value	0.6318		0.6691		0.8250	
Hedges' g	-0.07		0.10		0.02	
95% CI	[-0.59, 0.45]		[-0.46, 0.66]		[-0.36, 0.40]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_2_m_egfr_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	28.6 (8.20)	30.8 (8.60)	30.4 (8.69)	33.2 (9.84)	29.5 (8.42)	32.0 (9.23)
Visit 13/ET						
n/N2	42/42	22/22	37/37	22/23	79/79	44/45
Mean (SD)	28.3 (10.09)	31.1 (10.53)	28.7 (10.24)	31.5 (11.56)	28.5 (10.10)	31.3 (10.93)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.4 (1.01)	0.3 (1.40)	-1.7 (0.97)	-1.4 (1.27)	-1.0 (0.70)	-0.5 (0.94)
95% CI	[-2.40, 1.66]	[-2.46, 3.15]	[-3.67, 0.23]	[-3.91, 1.16]	[-2.44, 0.35]	[-2.38, 1.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.72		-0.34		-0.53	
95% CI	[-4.19, 2.76]		[-3.56, 2.87]		[-2.87, 1.81]	
p-value	0.6821		0.8313		0.6546	
Hedges' g	-0.09		-0.05		-0.07	
95% CI	[-0.60, 0.42]		[-0.57, 0.47]		[-0.43, 0.30]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_2_m_egfr_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	25.2 (8.78)	28.5 (8.87)	27.8 (8.95)	28.0 (6.49)	26.4 (8.89)	28.2 (7.54)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	26.1 (11.31)	27.4 (8.82)	25.3 (9.49)	25.6 (6.98)	25.7 (10.41)	26.4 (7.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.7 (1.31)	-1.2 (2.01)	-2.4 (0.93)	-1.3 (1.24)	-0.8 (0.80)	-1.3 (1.15)
95% CI	[-1.95, 3.31]		[-4.26, -0.54]		[-2.43, 0.75]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.88		-1.06		0.47	
95% CI	[-2.97, 6.73]		[-4.17, 2.05]		[-2.31, 3.25]	
p-value	0.4394		0.4967		0.7376	
Hedges' g	0.32		-0.21		0.11	
95% CI	[-0.26, 0.90]		[-0.77, 0.34]		[-0.29, 0.51]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_2_m_egfr_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.1.s6.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5736		0.8966		0.8782	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	26/36	19/23	30/48	9/16	56/84	28/39
Mean (SD)	0.8 (0.94)	0.5 (0.71)	0.6 (0.65)	0.5 (0.69)	0.7 (0.80)	0.5 (0.69)
Visit 13/ET						
n/N1	27/36	20/23	29/48	10/16	56/84	30/39
Mean (SD)	0.9 (1.33)	0.6 (1.02)	0.8 (1.14)	0.7 (0.90)	0.9 (1.23)	0.6 (0.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.13)	0.2 (0.15)	0.3 (0.17)	0.2 (0.30)	0.2 (0.10)	0.2 (0.15)
95% CI	[-0.14, 0.37]	[-0.10, 0.50]	[-0.03, 0.68]	[-0.39, 0.82]	[0.01, 0.43]	[-0.10, 0.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.09		0.11		0.02	
95% CI	[-0.49, 0.31]		[-0.59, 0.81]		[-0.35, 0.39]	
p-value	0.6615		0.7536		0.9310	
Hedges' g	-0.02		0.12		0.08	
95% CI	[-0.59, 0.55]		[-0.62, 0.87]		[-0.37, 0.52]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_15_1_1_m_ua_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.1.s6.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	33/42	19/22	31/37	18/23	64/79	37/45
Mean (SD)	0.5 (0.66)	0.9 (1.32)	0.8 (1.08)	0.4 (0.76)	0.7 (0.89)	0.7 (1.10)
Visit 13/ET						
n/N2	36/42	20/22	31/37	15/23	67/79	35/45
Mean (SD)	0.5 (0.76)	0.7 (0.88)	0.9 (1.10)	0.5 (0.81)	0.7 (0.95)	0.6 (0.84)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.09)	-0.1 (0.12)	0.1 (0.13)	-0.1 (0.19)	0.1 (0.08)	-0.1 (0.11)
95% CI	[-0.20, 0.17]	[-0.35, 0.15]	[-0.15, 0.39]	[-0.44, 0.33]	[-0.10, 0.21]	[-0.30, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.17		0.14	
95% CI	[-0.24, 0.40]		[-0.30, 0.65]		[-0.13, 0.41]	
p-value	0.6129		0.4652		0.3109	
Hedges' g	0.33		0.10		0.22	
95% CI	[-0.21, 0.88]		[-0.51, 0.71]		[-0.18, 0.63]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_15_1_1_m_ua_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.1.s6.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	34/37	15/17	28/34	19/21	62/71	34/38
Mean (SD)	0.6 (0.78)	0.6 (0.59)	0.8 (1.10)	1.3 (1.59)	0.7 (0.93)	1.0 (1.28)
Visit 13/ET						
n/N3	30/37	14/17	26/34	14/21	56/71	28/38
Mean (SD)	0.7 (0.98)	0.6 (0.73)	0.7 (0.91)	0.7 (0.57)	0.7 (0.94)	0.6 (0.64)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.12)	0.1 (0.18)	-0.1 (0.08)	-0.2 (0.11)	-0.0 (0.08)	-0.1 (0.11)
95% CI	[-0.20, 0.30]		[-0.28, 0.04]		[-0.18, 0.12]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.11		0.06	
95% CI	[-0.47, 0.42]		[-0.16, 0.38]		[-0.21, 0.32]	
p-value	0.9153		0.4201		0.6756	
Hedges' g	-0.06		0.30		0.11	
95% CI	[-0.68, 0.56]		[-0.34, 0.94]		[-0.34, 0.56]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_15_1_1_m_ua_ttlpth_pp.sas using SAS 9.4

Table 12.4.12.1.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5695		0.3878		0.2599	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	9.3 (0.33)	9.4 (0.36)	9.4 (0.36)	9.6 (0.19)	9.4 (0.35)	9.5 (0.30)
Visit 13/ET						
n/N1	13/13	5/5	26/27	3/4	39/40	8/9
Mean (SD)	9.7 (0.45)	9.5 (0.32)	9.8 (0.31)	9.6 (0.35)	9.8 (0.36)	9.5 (0.32)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.10)	0.1 (0.16)	0.4 (0.05)	0.1 (0.16)	0.3 (0.05)	0.1 (0.11)
95% CI	[0.14, 0.55]	[-0.25, 0.42]	[0.25, 0.47]	[-0.21, 0.43]	[0.24, 0.45]	[-0.13, 0.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.26		0.25		0.26	
95% CI	[-0.14, 0.66]		[-0.08, 0.59]		[0.01, 0.50]	
p-value	0.1864		0.1344		0.0415	
Hedges' g	0.76		1.01		0.92	
95% CI	[-0.26, 1.77]		[-0.18, 2.21]		[0.15, 1.69]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_1_m_dca_dose_pp.sas using SAS 9.4

Table 12.4.12.1.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	9.2 (0.26)	9.2 (0.26)	9.2 (0.28)	9.2 (0.26)	9.2 (0.27)	9.2 (0.26)
Visit 13/ET						
n/N2	102/102	56/57	91/92	54/56	193/194	110/113
Mean (SD)	9.4 (0.39)	9.3 (0.33)	9.5 (0.36)	9.3 (0.56)	9.4 (0.37)	9.3 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.03)	0.1 (0.04)	0.3 (0.04)	0.1 (0.05)	0.3 (0.03)	0.1 (0.03)
95% CI	[0.19, 0.32]	[0.03, 0.21]	[0.20, 0.36]	[0.01, 0.21]	[0.22, 0.32]	[0.05, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.17		0.15	
95% CI	[0.03, 0.24]		[0.04, 0.29]		[0.07, 0.23]	
p-value	0.0160		0.0091		0.0004	
Hedges' g	0.45		0.47		0.46	
95% CI	[0.12, 0.77]		[0.13, 0.81]		[0.22, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_1_m_dca_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4147		0.6452		0.4812	
Comparison Baseline vs. EAP	0.2014		0.7862		0.2994	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	3.4 (0.58)	3.2 (0.50)	3.8 (0.36)	3.5 (0.39)	3.7 (0.46)	3.3 (0.45)
Visit 13/ET						
n/N1	13/13	5/5	26/27	3/4	39/40	8/9
Mean (SD)	3.8 (0.58)	3.7 (0.76)	3.9 (0.59)	3.3 (0.66)	3.9 (0.58)	3.5 (0.70)
EAP						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	3.6 (0.56)	3.6 (0.40)	3.9 (0.48)	3.5 (0.47)	3.8 (0.53)	3.6 (0.41)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.16)	0.4 (0.26)	0.2 (0.10)	-0.2 (0.32)	0.2 (0.09)	0.1 (0.21)
95% CI	[0.01, 0.70]	[-0.17, 0.95]	[-0.04, 0.39]	[-0.87, 0.43]	[0.06, 0.44]	[-0.36, 0.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.40		0.19	
95% CI	[-0.69, 0.64]		[-0.30, 1.09]		[-0.26, 0.65]	
p-value	0.9257		0.2502		0.3982	
Hedges' g	-0.22		0.57		-0.04	
95% CI	[-1.21, 0.76]		[-0.60, 1.74]		[-0.79, 0.71]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.11)	0.4 (0.18)	0.2 (0.07)	0.0 (0.17)	0.2 (0.06)	0.2 (0.13)
95% CI	[-0.04, 0.43]	[-0.02, 0.74]	[0.05, 0.31]	[-0.33, 0.38]	[0.05, 0.30]	[-0.08, 0.43]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.17		0.16		0.00	
95% CI	[-0.62, 0.28]		[-0.23, 0.54]		[-0.28, 0.28]	
p-value	0.4407		0.4080		0.9945	
Hedges' g	-0.56		0.42		-0.20	
95% CI	[-1.56, 0.44]		[-0.61, 1.45]		[-0.91, 0.52]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	3.8 (0.53)	3.9 (0.57)	3.8 (0.62)	3.6 (0.45)	3.8 (0.57)	3.7 (0.52)
Visit 13/ET						
n/N2	102/102	56/57	91/92	54/56	193/194	110/113
Mean (SD)	3.9 (0.72)	3.9 (0.64)	4.1 (0.76)	3.7 (0.73)	4.0 (0.74)	3.8 (0.69)
EAP						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	3.9 (0.62)	3.9 (0.58)	4.0 (0.71)	3.8 (0.54)	4.0 (0.67)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.0 (0.08)	0.3 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.26]	[-0.11, 0.20]	[0.15, 0.41]	[-0.11, 0.23]	[0.13, 0.30]	[-0.06, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.22		0.16	
95% CI	[-0.09, 0.29]		[0.00, 0.43]		[0.02, 0.30]	
p-value	0.2907		0.0471		0.0266	
Hedges' g	0.21		0.28		0.24	
95% CI	[-0.12, 0.53]		[-0.06, 0.62]		[0.01, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.04)	0.1 (0.05)	0.3 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.06, 0.22]	[-0.00, 0.21]	[0.17, 0.37]	[-0.04, 0.23]	[0.14, 0.27]	[0.02, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.18		0.10	
95% CI	[-0.10, 0.17]		[0.01, 0.34]		[-0.00, 0.21]	
p-value	0.5925		0.0402		0.0582	
Hedges' g	0.13		0.27		0.20	
95% CI	[-0.20, 0.45]		[-0.06, 0.60]		[-0.03, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.5.1.1.1.s7.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	NA		NA		NA	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	8/13	2/5	13/27	2/4	21/40	4/9
Mean (SD)	37.6 (24.23)	82.8 (85.91)	39.4 (30.64)	21.1 (8.91)	38.7 (27.74)	51.9 (61.27)
Visit 13/ET						
n/N1	7/13	1/5	10/27	0/4	17/40	1/9
Mean (SD)	27.6 (13.83)	18.2 (NA)	58.2 (81.85)	NA (NA)	45.6 (63.89)	18.2 (NA)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-9.2 (5.73)	-19.5 (15.52)	21.6 (32.53)	NA (NA)	5.6 (17.27)	NA (NA)
95% CI	[-23.97, 5.48]	[-59.37, 20.40]	[-58.03, 101.15]	NA	[-32.01, 43.26]	NA
Diff in LS-Mean [ER-Calcifediol - Placebo]	10.24		NA		NA	
95% CI	[-32.56, 53.04]		NA		NA	
p-value	0.5654		NA		NA	
Hedges' g	NA		NA		NA	
95% CI	NA		NA		NA	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_5_1_1_1_m_fgf23_dose_pp.sas using SAS 9.4

Table 12.5.1.1.1.s7.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	72/102	33/57	56/92	37/56	128/194	70/113
Mean (SD)	48.4 (55.93)	40.5 (31.58)	33.3 (24.03)	34.8 (26.28)	41.8 (45.33)	37.5 (28.83)
Visit 13/ET						
n/N2	62/102	21/57	57/92	25/56	119/194	46/113
Mean (SD)	50.8 (49.16)	43.4 (31.72)	62.0 (69.45)	63.3 (58.33)	56.2 (59.75)	54.2 (48.59)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	6.1 (6.40)	-5.3 (10.79)	36.5 (11.74)	29.0 (16.22)	20.8 (6.33)	11.5 (9.61)
95% CI	[-6.61, 18.91]	[-26.80, 16.24]	[13.03, 60.04]	[-3.49, 61.45]	[8.25, 33.30]	[-7.49, 30.52]
Diff in LS-Mean [ER-Calcifediol - Placebo]	11.43		7.56		9.26	
95% CI	[-13.59, 36.45]		[-32.58, 47.70]		[-13.51, 32.04]	
p-value	0.3655		0.7075		0.4224	
Hedges' g	0.21		0.14		0.13	
95% CI	[-0.31, 0.73]		[-0.38, 0.66]		[-0.24, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_5_1_1_1_m_fgf23_dose_pp.sas using SAS 9.4

Table 12.4.12.1.2.s7.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1465		0.3945		0.6880	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	29.1 (8.51)	42.6 (13.48)	32.8 (9.60)	42.3 (8.54)	31.6 (9.32)	42.4 (10.88)
Visit 13/ET						
n/N1	13/13	5/5	26/27	3/4	39/40	8/9
Mean (SD)	29.0 (11.78)	37.8 (16.08)	32.2 (14.02)	45.7 (10.97)	31.1 (13.25)	40.8 (14.10)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.6 (1.63)	-6.6 (2.84)	-0.1 (1.59)	2.9 (4.84)	0.3 (1.25)	-1.8 (2.80)
95% CI	[-2.86, 4.08]	[-12.63, -0.55]	[-3.38, 3.17]	[-7.04, 12.87]	[-2.26, 2.78]	[-7.47, 3.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	7.20		-3.02		2.08	
95% CI	[-0.22, 14.62]		[-13.58, 7.54]		[-4.29, 8.44]	
p-value	0.0562		0.5614		0.5138	
Hedges' g	0.79		-0.55		0.16	
95% CI	[-0.22, 1.81]		[-1.72, 0.62]		[-0.59, 0.90]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_2_m_egfr_dose_pp.sas using SAS 9.4

Table 12.4.12.1.2.s7.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	30.5 (11.29)	32.5 (10.56)	30.2 (9.39)	31.8 (8.96)	30.3 (10.41)	32.2 (9.77)
Visit 13/ET						
n/N2	102/102	56/57	91/92	54/56	193/194	110/113
Mean (SD)	30.1 (11.86)	32.4 (11.01)	28.3 (10.23)	30.1 (10.10)	29.3 (11.13)	31.3 (10.59)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.72)	-0.1 (0.98)	-1.7 (0.58)	-1.5 (0.76)	-1.1 (0.47)	-0.8 (0.63)
95% CI	[-1.91, 0.95]	[-2.00, 1.87]	[-2.87, -0.57]	[-2.99, 0.00]	[-2.04, -0.18]	[-2.01, 0.45]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.42		-0.23		-0.33	
95% CI	[-2.83, 1.99]		[-2.12, 1.66]		[-1.87, 1.22]	
p-value	0.7339		0.8119		0.6750	
Hedges' g	0.00		-0.02		-0.00	
95% CI	[-0.32, 0.33]		[-0.36, 0.31]		[-0.24, 0.23]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_2_m_egfr_dose_pp.sas using SAS 9.4

Table 12.4.15.1.1.s7.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3375		NA		0.8571	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	11/13	5/5	19/27	1/4	30/40	6/9
Mean (SD)	0.8 (0.99)	0.1 (0.07)	0.5 (0.69)	5.7 (NA)	0.6 (0.80)	1.0 (2.30)
Visit 13/ET						
n/N1	10/13	5/5	16/27	1/4	26/40	6/9
Mean (SD)	0.6 (0.66)	0.1 (0.16)	0.8 (1.11)	0.4 (NA)	0.7 (0.96)	0.2 (0.18)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.14)	-0.2 (0.20)	0.2 (0.25)	-0.2 (0.99)	0.0 (0.16)	-0.2 (0.43)
95% CI	[-0.40, 0.21]	[-0.67, 0.21]	[-0.31, 0.76]	[-2.33, 1.93]	[-0.28, 0.37]	[-1.07, 0.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.14		0.42		0.23	
95% CI	[-0.41, 0.69]		[-1.77, 2.62]		[-0.72, 1.18]	
p-value	0.5904		0.6857		0.6202	
Hedges' g	-0.39		NA		0.07	
95% CI	[-1.41, 0.63]		NA		[-0.80, 0.93]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_15_1_1_m_ua_dose_pp.sas using SAS 9.4

Table 12.4.15.1.1.s7.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	82/102	48/57	70/92	45/56	152/194	93/113
Mean (SD)	0.6 (0.76)	0.7 (0.98)	0.8 (1.02)	0.7 (0.99)	0.7 (0.89)	0.7 (0.98)
Visit 13/ET						
n/N2	83/102	49/57	70/92	38/56	153/194	87/113
Mean (SD)	0.7 (1.06)	0.7 (0.91)	0.8 (1.05)	0.6 (0.75)	0.8 (1.05)	0.7 (0.84)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.0 (0.10)	0.1 (0.08)	-0.1 (0.11)	0.1 (0.06)	-0.0 (0.07)
95% CI	[-0.04, 0.25]	[-0.17, 0.20]	[-0.08, 0.25]	[-0.28, 0.16]	[-0.02, 0.20]	[-0.16, 0.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.14		0.11	
95% CI	[-0.15, 0.33]		[-0.13, 0.41]		[-0.07, 0.29]	
p-value	0.4656		0.2969		0.2428	
Hedges' g	0.14		0.16		0.15	
95% CI	[-0.21, 0.49]		[-0.24, 0.56]		[-0.12, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_15_1_1_m_ua_dose_pp.sas using SAS 9.4

Table 12.4.12.1.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1212		0.0297		0.7169	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	9.2 (0.27)	9.2 (0.23)	9.3 (0.32)	9.1 (0.27)	9.2 (0.30)	9.2 (0.24)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	9.3 (0.45)	9.3 (0.34)	9.7 (0.43)	9.1 (0.47)	9.5 (0.48)	9.2 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	0.1 (0.12)	0.5 (0.07)	-0.0 (0.12)	0.3 (0.06)	0.1 (0.08)
95% CI	[-0.10, 0.32]	[-0.12, 0.39]	[0.31, 0.62]	[-0.25, 0.23]	[0.17, 0.41]	[-0.12, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.48		0.24	
95% CI	[-0.35, 0.30]		[0.19, 0.76]		[0.02, 0.45]	
p-value	0.8777		0.0023		0.0300	
Hedges' g	-0.08		1.46		0.61	
95% CI	[-0.85, 0.70]		[0.57, 2.35]		[0.04, 1.19]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_1_m_dca_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	9.2 (0.28)	9.3 (0.28)	9.2 (0.32)	9.3 (0.27)	9.2 (0.30)	9.3 (0.28)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	9.5 (0.39)	9.3 (0.33)	9.5 (0.36)	9.4 (0.55)	9.5 (0.37)	9.4 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.03)	0.1 (0.05)	0.3 (0.04)	0.1 (0.05)	0.3 (0.02)	0.1 (0.03)
95% CI	[0.22, 0.35]	[0.02, 0.20]	[0.20, 0.34]	[0.03, 0.23]	[0.23, 0.33]	[0.05, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.14		0.16	
95% CI	[0.07, 0.29]		[0.01, 0.26]		[0.08, 0.24]	
p-value	0.0018		0.0303		0.0002	
Hedges' g	0.59		0.40		0.50	
95% CI	[0.25, 0.93]		[0.06, 0.75]		[0.25, 0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_1_m_dca_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1984		0.8259		0.4794	
Comparison Baseline vs. EAP	0.7725		0.7347		0.8110	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	3.6 (0.40)	3.9 (0.50)	3.8 (0.54)	4.0 (0.45)	3.7 (0.49)	4.0 (0.47)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	3.8 (0.45)	3.8 (0.64)	4.1 (1.03)	4.2 (0.64)	4.0 (0.83)	3.9 (0.65)
EAP						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	3.7 (0.40)	4.0 (0.38)	4.1 (0.84)	4.2 (0.46)	3.9 (0.71)	4.1 (0.42)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.13)	-0.1 (0.16)	0.3 (0.19)	0.2 (0.30)	0.2 (0.12)	0.0 (0.17)
95% CI	[-0.15, 0.38]	[-0.42, 0.24]	[-0.06, 0.74]	[-0.41, 0.83]	[-0.01, 0.48]	[-0.29, 0.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.21		0.13		0.19	
95% CI	[-0.23, 0.64]		[-0.61, 0.88]		[-0.23, 0.61]	
p-value	0.3395		0.7128		0.3737	
Hedges' g	0.66		0.19		0.41	
95% CI	[-0.14, 1.45]		[-0.61, 0.99]		[-0.16, 0.98]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-0.0 (0.09)	0.2 (0.11)	0.3 (0.14)	0.3 (0.22)	0.2 (0.09)	0.2 (0.12)
95% CI	[-0.20, 0.17]	[-0.06, 0.40]	[0.05, 0.63]	[-0.17, 0.73]	[-0.00, 0.35]	[-0.03, 0.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.18		0.06		-0.04	
95% CI	[-0.49, 0.12]		[-0.48, 0.60]		[-0.35, 0.27]	
p-value	0.2263		0.8196		0.8013	
Hedges' g	-0.04		0.13		0.11	
95% CI	[-0.82, 0.73]		[-0.67, 0.93]		[-0.45, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	3.7 (0.56)	3.8 (0.61)	3.8 (0.58)	3.6 (0.42)	3.8 (0.57)	3.7 (0.53)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	3.9 (0.74)	3.9 (0.66)	4.0 (0.66)	3.6 (0.72)	4.0 (0.70)	3.8 (0.69)
EAP						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	3.9 (0.64)	3.9 (0.60)	4.0 (0.63)	3.7 (0.51)	4.0 (0.64)	3.8 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.2 (0.06)	0.0 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.06, 0.29]	[-0.04, 0.28]	[0.13, 0.35]	[-0.14, 0.18]	[0.13, 0.29]	[-0.04, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.22		0.14	
95% CI	[-0.15, 0.25]		[0.03, 0.42]		[-0.00, 0.28]	
p-value	0.6181		0.0254		0.0517	
Hedges' g	0.09		0.29		0.19	
95% CI	[-0.24, 0.43]		[-0.05, 0.63]		[-0.05, 0.43]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.06)	0.2 (0.04)	0.1 (0.06)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.08, 0.25]	[0.02, 0.25]	[0.15, 0.33]	[-0.07, 0.18]	[0.14, 0.26]	[0.02, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		0.18		0.10	
95% CI	[-0.11, 0.17]		[0.03, 0.34]		[-0.00, 0.20]	
p-value	0.6971		0.0188		0.0555	
Hedges' g	0.08		0.28		0.19	
95% CI	[-0.25, 0.41]		[-0.05, 0.62]		[-0.05, 0.42]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s8.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4523		0.5276		0.4584	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	11/15	5/10	11/19	3/8	22/34	8/18
Mean (SD)	59.2 (44.32)	43.0 (42.80)	29.8 (25.13)	48.1 (37.78)	44.5 (38.24)	44.9 (38.23)
Visit 13/ET						
n/N1	8/15	2/10	12/19	3/8	20/34	5/18
Mean (SD)	59.6 (28.39)	61.6 (34.29)	75.8 (113.15)	67.2 (44.27)	69.3 (88.18)	65.0 (35.83)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.6 (13.08)	7.6 (26.20)	75.8 (50.36)	22.9 (78.03)	43.0 (26.17)	12.7 (46.73)
95% CI	[-23.36, 40.65]	[-56.54, 71.70]	[-43.27, 194.89]	[-161.57, 207.44]	[-13.09, 99.18]	[-87.53, 112.91]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.06		52.88		30.36	
95% CI	[-73.48, 75.61]		[-169.95, 275.71]		[-87.50, 148.23]	
p-value	0.9733		0.5922		0.5893	
Hedges' g	0.72		0.43		0.44	
95% CI	[-0.72, 2.16]		[-0.81, 1.66]		[-0.55, 1.42]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_5_1_1_1_m_fgf23_vitd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s8.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	69/100	30/52	58/100	36/52	127/200	66/104
Mean (SD)	45.4 (54.98)	42.9 (34.91)	35.3 (25.41)	32.9 (24.96)	40.8 (44.15)	37.5 (30.07)
Visit 13/ET						
n/N2	61/100	20/52	55/100	22/52	116/200	42/104
Mean (SD)	47.0 (49.19)	40.4 (31.40)	58.3 (58.80)	62.7 (60.82)	52.4 (54.02)	52.1 (49.79)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	3.5 (6.40)	-6.6 (11.09)	27.8 (10.15)	28.0 (15.32)	15.3 (5.77)	10.3 (9.28)
95% CI	[-9.24, 16.30]	[-28.72, 15.51]	[7.46, 48.14]	[-2.74, 58.66]	[3.88, 26.70]	[-8.09, 28.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	10.13		-0.16		5.02	
95% CI	[-15.40, 35.67]		[-36.99, 36.66]		[-16.60, 26.64]	
p-value	0.4313		0.9930		0.6469	
Hedges' g	0.13		-0.01		0.04	
95% CI	[-0.39, 0.66]		[-0.56, 0.54]		[-0.34, 0.42]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_5_1_1_1_m_fgf23_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0993		0.9596		0.3536	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	26.3 (8.03)	34.3 (13.65)	31.5 (9.75)	25.8 (6.23)	29.2 (9.27)	30.5 (11.56)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	29.1 (11.54)	32.8 (12.00)	28.9 (13.27)	23.4 (7.69)	29.0 (12.36)	28.6 (11.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	2.7 (1.61)	-1.3 (2.00)	-2.9 (1.31)	-1.6 (2.06)	0.2 (1.02)	-2.0 (1.40)
95% CI	[-0.69, 6.00]	[-5.44, 2.87]	[-5.62, -0.19]	[-5.86, 2.66]	[-1.90, 2.21]	[-4.78, 0.86]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.94		-1.31		2.11	
95% CI	[-1.56, 9.44]		[-6.45, 3.84]		[-1.38, 5.61]	
p-value	0.1517		0.6051		0.2295	
Hedges' g	0.70		-0.03		0.27	
95% CI	[-0.10, 1.50]		[-0.84, 0.77]		[-0.30, 0.83]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_2_m_egfr_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	30.9 (11.28)	33.1 (10.63)	30.7 (9.45)	33.5 (9.24)	30.8 (10.38)	33.3 (9.91)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	30.1 (11.89)	32.9 (11.44)	29.2 (10.88)	32.1 (10.61)	29.7 (11.38)	32.5 (10.99)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.9 (0.74)	-0.3 (1.03)	-1.2 (0.62)	-1.0 (0.88)	-1.1 (0.48)	-0.6 (0.68)
95% CI	[-2.37, 0.54]	[-2.31, 1.77]	[-2.40, 0.06]	[-2.73, 0.76]	[-2.01, -0.10]	[-1.94, 0.75]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.65		-0.18		-0.46	
95% CI	[-3.16, 1.87]		[-2.33, 1.96]		[-2.11, 1.20]	
p-value	0.6131		0.8667		0.5873	
Hedges' g	-0.03		-0.01		-0.02	
95% CI	[-0.36, 0.31]		[-0.35, 0.33]		[-0.26, 0.22]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_2_m_egfr_vitd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s8.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6552		0.2158		0.1931	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	13/15	8/10	13/19	7/8	26/34	15/18
Mean (SD)	0.8 (1.00)	0.5 (0.93)	1.0 (1.28)	0.7 (0.77)	0.9 (1.14)	0.6 (0.84)
Visit 13/ET						
n/N1	10/15	7/10	12/19	5/8	22/34	12/18
Mean (SD)	0.8 (0.71)	0.2 (0.37)	1.3 (1.44)	0.6 (0.78)	1.1 (1.17)	0.4 (0.57)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.14)	-0.5 (0.17)	0.2 (0.22)	-0.4 (0.34)	0.1 (0.14)	-0.4 (0.19)
95% CI	[-0.34, 0.26]	[-0.81, -0.10]	[-0.23, 0.70]	[-1.11, 0.32]	[-0.21, 0.37]	[-0.80, -0.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.41		0.63		0.48	
95% CI	[-0.06, 0.88]		[-0.23, 1.48]		[-0.01, 0.98]	
p-value	0.0805		0.1377		0.0549	
Hedges' g	0.27		0.80		0.57	
95% CI	[-0.65, 1.19]		[-0.23, 1.82]		[-0.13, 1.27]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_15_1_1_m_ua_vitd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s8.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	80/100	45/52	76/100	39/52	156/200	84/104
Mean (SD)	0.6 (0.75)	0.7 (0.97)	0.7 (0.89)	0.8 (1.30)	0.6 (0.82)	0.8 (1.13)
Visit 13/ET						
n/N2	83/100	47/52	74/100	34/52	157/200	81/104
Mean (SD)	0.7 (1.06)	0.7 (0.92)	0.7 (0.97)	0.6 (0.75)	0.7 (1.02)	0.7 (0.85)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.1 (0.09)	0.1 (0.08)	-0.0 (0.12)	0.1 (0.06)	0.0 (0.08)
95% CI	[-0.05, 0.23]	[-0.12, 0.25]	[-0.08, 0.25]	[-0.25, 0.23]	[-0.02, 0.20]	[-0.12, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		0.09		0.05	
95% CI	[-0.21, 0.26]		[-0.20, 0.39]		[-0.13, 0.24]	
p-value	0.8257		0.5219		0.5759	
Hedges' g	0.04		0.10		0.07	
95% CI	[-0.31, 0.40]		[-0.31, 0.51]		[-0.20, 0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_15_1_1_m_ua_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4920		0.3086		0.8023	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	9.2 (0.28)	9.2 (0.28)	9.2 (0.29)	9.3 (0.21)	9.2 (0.29)	9.3 (0.25)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	9.5 (0.40)	9.3 (0.34)	9.5 (0.39)	9.4 (0.61)	9.5 (0.39)	9.3 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.2 (0.05)	0.1 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.17, 0.35]	[-0.04, 0.19]	[0.15, 0.35]	[-0.05, 0.25]	[0.19, 0.32]	[-0.00, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.15		0.16	
95% CI	[0.04, 0.33]		[-0.03, 0.33]		[0.05, 0.28]	
p-value	0.0132		0.1044		0.0057	
Hedges' g	0.58		0.38		0.49	
95% CI	[0.15, 1.00]		[-0.07, 0.84]		[0.17, 0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_1_m_dca_bl25d_pp.sas using SAS 9.4

Table 12.4.12.1.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	9.2 (0.27)	9.2 (0.27)	9.3 (0.34)	9.2 (0.32)	9.2 (0.31)	9.2 (0.29)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	9.5 (0.40)	9.4 (0.31)	9.6 (0.35)	9.3 (0.49)	9.5 (0.38)	9.4 (0.41)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.2 (0.06)	0.4 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.18, 0.36]	[0.04, 0.29]	[0.28, 0.45]	[-0.02, 0.22]	[0.26, 0.38]	[0.04, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.26		0.19	
95% CI	[-0.05, 0.26]		[0.12, 0.41]		[0.08, 0.29]	
p-value	0.1768		0.0006		0.0006	
Hedges' g	0.36		0.72		0.54	
95% CI	[-0.10, 0.81]		[0.27, 1.16]		[0.22, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_1_m_dca_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8111		0.6301		0.8718	
Comparison Baseline vs. EAP	0.6859		0.5962		0.8725	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	3.8 (0.50)	3.7 (0.58)	3.8 (0.62)	3.6 (0.41)	3.8 (0.56)	3.7 (0.51)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	3.9 (0.68)	3.7 (0.60)	4.1 (0.86)	3.8 (0.76)	4.0 (0.78)	3.8 (0.67)
EAP						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	3.9 (0.53)	3.8 (0.57)	4.1 (0.78)	3.8 (0.55)	4.0 (0.67)	3.8 (0.55)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.0 (0.10)	0.3 (0.08)	0.2 (0.12)	0.2 (0.06)	0.1 (0.08)
95% CI	[0.03, 0.33]	[-0.19, 0.21]	[0.14, 0.47]	[-0.06, 0.42]	[0.13, 0.36]	[-0.06, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.13		0.15	
95% CI	[-0.08, 0.42]		[-0.17, 0.42]		[-0.04, 0.35]	
p-value	0.1765		0.4005		0.1226	
Hedges' g	0.21		0.19		0.21	
95% CI	[-0.21, 0.63]		[-0.26, 0.64]		[-0.10, 0.52]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.3 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.24]	[-0.01, 0.25]	[0.16, 0.43]	[-0.09, 0.29]	[0.14, 0.30]	[-0.00, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.19		0.11	
95% CI	[-0.14, 0.19]		[-0.03, 0.42]		[-0.03, 0.25]	
p-value	0.7812		0.0952		0.1126	
Hedges' g	0.01		0.34		0.19	
95% CI	[-0.41, 0.42]		[-0.10, 0.78]		[-0.11, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	3.7 (0.58)	3.9 (0.59)	3.8 (0.53)	3.6 (0.47)	3.7 (0.55)	3.8 (0.55)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	3.9 (0.74)	4.0 (0.67)	3.9 (0.56)	3.6 (0.68)	3.9 (0.65)	3.8 (0.71)
EAP						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	3.8 (0.70)	4.0 (0.57)	4.0 (0.54)	3.7 (0.53)	3.9 (0.63)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.11)	0.2 (0.07)	-0.1 (0.10)	0.2 (0.05)	0.1 (0.07)
95% CI	[0.01, 0.31]	[-0.07, 0.36]	[0.07, 0.35]	[-0.27, 0.13]	[0.07, 0.28]	[-0.09, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.28		0.12	
95% CI	[-0.25, 0.28]		[0.03, 0.53]		[-0.06, 0.30]	
p-value	0.9122		0.0259		0.1873	
Hedges' g	0.13		0.34		0.25	
95% CI	[-0.32, 0.58]		[-0.09, 0.78]		[-0.07, 0.56]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.09)	0.2 (0.06)	0.1 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.27]	[-0.04, 0.30]	[0.10, 0.32]	[-0.08, 0.23]	[0.09, 0.25]	[0.01, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.13		0.05	
95% CI	[-0.19, 0.23]		[-0.06, 0.32]		[-0.08, 0.19]	
p-value	0.8431		0.1839		0.4409	
Hedges' g	0.13		0.17		0.16	
95% CI	[-0.32, 0.59]		[-0.26, 0.61]		[-0.16, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.5.1.1.1.s9.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5049		0.8096		0.9927	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	39/58	20/35	35/59	21/30	74/117	41/65
Mean (SD)	40.8 (35.51)	45.0 (34.76)	31.3 (21.11)	32.3 (24.88)	36.4 (29.78)	38.5 (30.41)
Visit 13/ET						
n/N1	36/58	13/35	36/59	16/30	72/117	29/65
Mean (SD)	35.6 (26.48)	35.4 (28.71)	62.7 (79.30)	60.9 (68.09)	49.2 (60.27)	49.5 (54.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (4.94)	-4.3 (8.03)	36.9 (16.19)	32.1 (22.45)	19.4 (8.10)	11.6 (12.09)
95% CI	[-9.83, 10.13]	[-20.48, 11.97]	[4.06, 69.78]	[-13.48, 77.66]	[3.27, 35.52]	[-12.54, 35.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	4.40		4.84		7.85	
95% CI	[-14.84, 23.65]		[-51.35, 61.02]		[-21.23, 36.92]	
p-value	0.6461		0.8623		0.5925	
Hedges' g	0.42		0.06		0.11	
95% CI	[-0.24, 1.08]		[-0.60, 0.71]		[-0.36, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_5_1_1_1_m_fgf23_bl25d_pp.sas using SAS 9.4

Table 12.5.1.1.1.s9.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	41/57	15/27	34/60	18/30	75/117	33/57
Mean (SD)	53.5 (66.32)	40.1 (37.32)	37.6 (28.90)	36.2 (27.40)	46.3 (53.04)	38.0 (31.82)
Visit 13/ET						
n/N2	33/57	9/27	31/60	9/30	64/117	18/57
Mean (SD)	62.4 (59.94)	52.3 (34.13)	60.0 (60.64)	67.4 (38.49)	61.2 (59.81)	59.9 (36.14)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.2 (10.76)	-6.4 (20.84)	30.7 (12.54)	24.7 (21.30)	19.0 (8.30)	7.2 (14.97)
95% CI	[-13.68, 29.99]	[-48.67, 35.96]	[4.97, 56.34]	[-18.95, 68.29]	[2.40, 35.54]	[-22.74, 37.06]
Diff in LS-Mean [ER-Calcifediol - Placebo]	14.51		5.98		11.81	
95% CI	[-33.13, 62.14]		[-44.70, 56.67]		[-22.37, 45.99]	
p-value	0.5404		0.8107		0.4926	
Hedges' g	0.08		0.18		0.11	
95% CI	[-0.69, 0.84]		[-0.60, 0.97]		[-0.45, 0.66]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_5_1_1_1_m_fgf23_bl25d_pp.sas using SAS 9.4

Table 12.4.12.1.2.s9.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1035		0.6871		0.1454	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	29.9 (11.56)	33.7 (11.94)	30.4 (9.88)	31.2 (8.51)	30.2 (10.70)	32.5 (10.49)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	30.0 (12.51)	32.1 (11.63)	28.3 (11.00)	28.2 (9.35)	29.2 (11.76)	30.4 (10.77)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.2 (1.07)	-1.4 (1.41)	-1.7 (0.75)	-2.0 (1.10)	-0.9 (0.66)	-1.8 (0.92)
95% CI	[-2.38, 1.89]	[-4.23, 1.37]	[-3.22, -0.23]	[-4.22, 0.16]	[-2.25, 0.36]	[-3.63, 0.00]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.19		0.31		0.87	
95% CI	[-2.36, 4.73]		[-2.34, 2.95]		[-1.37, 3.11]	
p-value	0.5074		0.8192		0.4450	
Hedges' g	0.24		0.05		0.16	
95% CI	[-0.18, 0.67]		[-0.40, 0.51]		[-0.15, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_2_m_egfr_bl25d_pp.sas using SAS 9.4

Table 12.4.12.1.2.s9.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	30.7 (10.47)	32.9 (9.98)	31.2 (9.10)	33.8 (9.90)	30.9 (9.75)	33.4 (9.86)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	30.0 (11.14)	33.8 (11.31)	29.9 (11.51)	33.3 (11.30)	30.0 (11.28)	33.5 (11.21)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.8 (0.79)	1.0 (1.14)	-1.0 (0.84)	-0.6 (1.19)	-0.9 (0.58)	0.3 (0.83)
95% CI	[-2.32, 0.81]	[-1.23, 3.32]	[-2.68, 0.67]	[-2.92, 1.80]	[-2.03, 0.25]	[-1.38, 1.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-1.80		-0.45		-1.14	
95% CI	[-4.57, 0.97]		[-3.36, 2.47]		[-3.14, 0.85]	
p-value	0.1998		0.7618		0.2600	
Hedges' g	-0.27		-0.07		-0.16	
95% CI	[-0.73, 0.18]		[-0.51, 0.36]		[-0.48, 0.15]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_2_m_egfr_bl25d_pp.sas using SAS 9.4

Table 12.4.15.1.1.s9.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5900		0.5098		0.9105	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	51/58	33/35	47/59	24/30	98/117	57/65
Mean (SD)	0.7 (0.78)	0.7 (0.97)	0.8 (1.08)	1.0 (1.45)	0.7 (0.93)	0.8 (1.20)
Visit 13/ET						
n/N1	53/58	31/35	45/59	20/30	98/117	51/65
Mean (SD)	0.7 (1.07)	0.6 (0.82)	0.9 (1.12)	0.8 (0.80)	0.8 (1.09)	0.7 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.10)	-0.1 (0.12)	0.1 (0.11)	0.0 (0.17)	0.1 (0.07)	-0.0 (0.10)
95% CI	[-0.14, 0.24]	[-0.30, 0.19]	[-0.15, 0.27]	[-0.32, 0.34]	[-0.09, 0.20]	[-0.23, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.05		0.08	
95% CI	[-0.21, 0.42]		[-0.34, 0.45]		[-0.17, 0.33]	
p-value	0.5080		0.7831		0.5322	
Hedges' g	0.16		0.07		0.13	
95% CI	[-0.28, 0.60]		[-0.46, 0.60]		[-0.21, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_15_1_1_m_ua_bl25d_pp.sas using SAS 9.4

Table 12.4.15.1.1.s9.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	42/57	20/27	42/60	22/30	84/117	42/57
Mean (SD)	0.6 (0.81)	0.6 (0.95)	0.6 (0.80)	0.6 (0.88)	0.6 (0.80)	0.6 (0.90)
Visit 13/ET						
n/N2	40/57	23/27	41/60	19/30	81/117	42/57
Mean (SD)	0.7 (0.98)	0.7 (0.98)	0.7 (0.98)	0.4 (0.64)	0.7 (0.98)	0.6 (0.85)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	0.1 (0.13)	0.2 (0.11)	-0.1 (0.16)	0.1 (0.08)	-0.0 (0.10)
95% CI	[-0.10, 0.29]	[-0.15, 0.36]	[-0.06, 0.40]	[-0.44, 0.21]	[-0.02, 0.28]	[-0.21, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.28		0.13	
95% CI	[-0.33, 0.31]		[-0.12, 0.68]		[-0.12, 0.38]	
p-value	0.9425		0.1595		0.3029	
Hedges' g	-0.03		0.33		0.15	
95% CI	[-0.53, 0.48]		[-0.22, 0.88]		[-0.22, 0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_15_1_1_m_ua_bl25d_pp.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalysen zu den Sicherheitsendpunkten (Unerwünschte Ereignisse (ITT-Population))

Folgende Daten werden für die ITT-Population:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (akutes Nierenversagen, Herzerkrankung
  - UE ohne erkrankungsbezogene Ereignisse

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.9089		0.6225		0.7477	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	43/59 (72.9)	24/30 (80.0)	32/50 (64.0)	21/32 (65.6)	75/109 (68.8)	45/62 (72.6)
RR [95%-CI]; p-value	0.91 [0.72, 1.15], 0.4412		0.98 [0.70, 1.35], 0.8801		0.95 [0.78, 1.16], 0.5980	
OR [95%-CI]; p-value	0.67 [0.23, 1.94], 0.4618		0.93 [0.37, 2.36], 0.8807		0.83 [0.42, 1.66], 0.6041	
RD [95%-CI]; p-value	-0.07 [-0.25, 0.11], 0.4449		-0.02 [-0.23, 0.20], 0.8804		-0.04 [-0.18, 0.10], 0.6001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	58/82 (70.7)	32/42 (76.2)	59/94 (62.8)	23/40 (57.5)	117/176 (66.5)	55/82 (67.1)
RR [95%-CI]; p-value	0.93 [0.75, 1.16], 0.5059		1.09 [0.80, 1.49], 0.5778		0.99 [0.82, 1.19], 0.9244	
OR [95%-CI]; p-value	0.76 [0.32, 1.78], 0.5190		1.25 [0.59, 2.65], 0.5670		0.97 [0.56, 1.70], 0.9247	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.11], 0.5093		0.05 [-0.13, 0.23], 0.5700		-0.01 [-0.13, 0.12], 0.9246	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.4501		0.8354		0.7728	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	7/59 (11.9)	6/30 (20.0)	9/50 (18.0)	1/32 (3.1)	16/109 (14.7)	7/62 (11.3)
RR [95%-CI]; p-value	0.59 [0.22, 1.61], 0.3051		5.76 [0.77, 43.32], 0.0890		1.30 [0.57, 2.99], 0.5362	
OR [95%-CI]; p-value	0.54 [0.16, 1.78], 0.3043		6.80 [0.82, 56.58], 0.0446		1.35 [0.52, 3.49], 0.5324	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.08], 0.3345		0.15 [0.03, 0.27], 0.0172		0.03 [-0.07, 0.14], 0.5193	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	5/42 (11.9)	10/94 (10.6)	1/40 (2.5)	20/176 (11.4)	6/82 (7.3)
RR [95%-CI]; p-value	1.02 [0.37, 2.80], 0.9626		4.26 [0.56, 32.14], 0.1604		1.55 [0.65, 3.72], 0.3235	
OR [95%-CI]; p-value	1.03 [0.33, 3.23], 0.9626		4.64 [0.57, 37.55], 0.1163		1.62 [0.63, 4.21], 0.3147	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9624		0.08 [0.00, 0.16], 0.0432		0.04 [-0.03, 0.11], 0.2794	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.2381		0.8988		0.4003	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	0/30 (0.0)	5/50 (10.0)	4/32 (12.5)	11/109 (10.1)	4/62 (6.5)
RR [95%-CI]; p-value	6.20 [0.36, 107.42], 0.2097		0.80 [0.23, 2.76], 0.7238		1.56 [0.52, 4.70], 0.4258	
OR [95%-CI]; p-value	6.79 [0.37, 125.88], 0.1405		0.78 [0.19, 3.14], 0.7239		1.63 [0.50, 5.35], 0.4185	
RD [95%-CI]; p-value	0.09 [-0.00, 0.17], 0.0612		-0.03 [-0.17, 0.12], 0.7293		0.04 [-0.05, 0.12], 0.3917	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	12/82 (14.6)	6/42 (14.3)	5/94 (5.3)	3/40 (7.5)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	1.02 [0.41, 2.54], 0.9585		0.71 [0.18, 2.83], 0.6262		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	1.03 [0.36, 2.97], 0.9584		0.69 [0.16, 3.05], 0.6259		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	0.00 [-0.13, 0.13], 0.9583		-0.02 [-0.12, 0.07], 0.6472		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.1929		0.4601		0.7152	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	11/59 (18.6)	2/30 (6.7)	9/50 (18.0)	7/32 (21.9)	20/109 (18.3)	9/62 (14.5)
RR [95%-CI]; p-value	2.80 [0.66, 11.82], 0.1619		0.82 [0.34, 1.99], 0.6650		1.26 [0.61, 2.60], 0.5249	
OR [95%-CI]; p-value	3.21 [0.66, 15.53], 0.1304		0.78 [0.26, 2.37], 0.6658		1.32 [0.56, 3.12], 0.5209	
RD [95%-CI]; p-value	0.12 [-0.01, 0.25], 0.0788		-0.04 [-0.22, 0.14], 0.6705		0.04 [-0.08, 0.15], 0.5095	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	19/82 (23.2)	10/42 (23.8)	13/94 (13.8)	4/40 (10.0)	32/176 (18.2)	14/82 (17.1)
RR [95%-CI]; p-value	0.97 [0.50, 1.90], 0.9365		1.38 [0.48, 3.98], 0.5480		1.06 [0.60, 1.88], 0.8290	
OR [95%-CI]; p-value	0.97 [0.40, 2.32], 0.9366		1.44 [0.44, 4.74], 0.5422		1.08 [0.54, 2.15], 0.8285	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.15], 0.9368		0.04 [-0.08, 0.15], 0.5185		0.01 [-0.09, 0.11], 0.8270	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9445		0.1812		0.2216	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	3/59 (5.1)	1/30 (3.3)	6/50 (12.0)	4/32 (12.5)	9/109 (8.3)	5/62 (8.1)
RR [95%-CI]; p-value	1.53 [0.17, 14.05], 0.7093		0.96 [0.29, 3.14], 0.9462		1.02 [0.36, 2.92], 0.9648	
OR [95%-CI]; p-value	1.55 [0.15, 15.61], 0.7062		0.95 [0.25, 3.69], 0.9462		1.03 [0.33, 3.21], 0.9648	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6872		-0.01 [-0.15, 0.14], 0.9464		0.00 [-0.08, 0.09], 0.9647	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	13/82 (15.9)	4/42 (9.5)	9/94 (9.6)	0/40 (0.0)	22/176 (12.5)	4/82 (4.9)
RR [95%-CI]; p-value	1.66 [0.58, 4.79], 0.3448		7.76 [0.46, 130.61], 0.1551		2.56 [0.91, 7.20], 0.0741	
OR [95%-CI]; p-value	1.79 [0.55, 5.87], 0.3321		8.47 [0.48, 149.76], 0.0833		2.79 [0.93, 8.37], 0.0583	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.2966		0.08 [0.01, 0.15], 0.0170		0.08 [0.01, 0.14], 0.0270	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.7704		0.3169		0.2523	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	0/30 (0.0)	3/50 (6.0)	3/32 (9.4)	4/109 (3.7)	3/62 (4.8)
RR [95%-CI]; p-value	1.03 [0.04, 29.96], 0.9845		0.64 [0.14, 2.98], 0.5694		0.76 [0.18, 3.28], 0.7112	
OR [95%-CI]; p-value	1.03 [0.03, 31.73], 0.9845		0.62 [0.12, 3.26], 0.5670		0.75 [0.16, 3.46], 0.7107	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9844		-0.03 [-0.15, 0.09], 0.5832		-0.01 [-0.08, 0.05], 0.7204	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	7/82 (8.5)	2/42 (4.8)	4/94 (4.3)	0/40 (0.0)	11/176 (6.3)	2/82 (2.4)
RR [95%-CI]; p-value	1.79 [0.39, 8.25], 0.4537		3.45 [0.19, 63.70], 0.4057		2.56 [0.58, 11.30], 0.2138	
OR [95%-CI]; p-value	1.87 [0.37, 9.41], 0.4432		3.56 [0.18, 68.85], 0.3715		2.67 [0.58, 12.32], 0.1926	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4024		0.03 [-0.02, 0.08], 0.2650		0.04 [-0.01, 0.09], 0.1268	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.9965		0.6373		0.7642	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	0/30 (0.0)	1/50 (2.0)	1/32 (3.1)	2/109 (1.8)	1/62 (1.6)
RR [95%-CI]; p-value	1.03 [0.04, 29.96], 0.9845		0.64 [0.04, 9.87], 0.7492		1.14 [0.11, 12.29], 0.9154	
OR [95%-CI]; p-value	1.03 [0.03, 31.73], 0.9845		0.63 [0.04, 10.49], 0.7473		1.14 [0.10, 12.83], 0.9154	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9844		-0.01 [-0.08, 0.06], 0.7584		0.00 [-0.04, 0.04], 0.9139	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	2/82 (2.4)	1/42 (2.4)	2/94 (2.1)	0/40 (0.0)	4/176 (2.3)	1/82 (1.2)
RR [95%-CI]; p-value	1.02 [0.10, 10.97], 0.9841		1.72 [0.08, 37.39], 0.7288		1.86 [0.21, 16.41], 0.5749	
OR [95%-CI]; p-value	1.03 [0.09, 11.64], 0.9841		1.74 [0.08, 39.43], 0.7250		1.88 [0.21, 17.12], 0.5677	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9840		0.01 [-0.04, 0.05], 0.6960		0.01 [-0.02, 0.04], 0.5239	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.3468		0.4116		0.8568	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	37/59 (62.7)	20/30 (66.7)	23/50 (46.0)	17/32 (53.1)	60/109 (55.0)	37/62 (59.7)
RR [95%-CI]; p-value	0.94 [0.68, 1.30], 0.7084		0.87 [0.56, 1.35], 0.5239		0.92 [0.71, 1.20], 0.5514	
OR [95%-CI]; p-value	0.84 [0.33, 2.12], 0.7132		0.75 [0.31, 1.83], 0.5289		0.83 [0.44, 1.56], 0.5568	
RD [95%-CI]; p-value	-0.04 [-0.25, 0.17], 0.7107		-0.07 [-0.29, 0.15], 0.5280		-0.05 [-0.20, 0.11], 0.5548	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	45/82 (54.9)	30/42 (71.4)	47/94 (50.0)	18/40 (45.0)	92/176 (52.3)	48/82 (58.5)
RR [95%-CI]; p-value	0.77 [0.58, 1.01], 0.0594		1.11 [0.75, 1.65], 0.6037		0.89 [0.71, 1.12], 0.3358	
OR [95%-CI]; p-value	0.49 [0.22, 1.08], 0.0744		1.22 [0.58, 2.57], 0.5961		0.78 [0.46, 1.32], 0.3470	
RD [95%-CI]; p-value	-0.17 [-0.34, 0.01], 0.0622		0.05 [-0.13, 0.23], 0.5950		-0.06 [-0.19, 0.07], 0.3438	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.1462		0.9378		0.4282	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	16/59 (27.1)	13/30 (43.3)	20/50 (40.0)	9/32 (28.1)	36/109 (33.0)	22/62 (35.5)
RR [95%-CI]; p-value	0.63 [0.35, 1.12], 0.1165		1.42 [0.74, 2.72], 0.2879		0.93 [0.61, 1.43], 0.7432	
OR [95%-CI]; p-value	0.49 [0.19, 1.22], 0.1229		1.70 [0.65, 4.43], 0.2726		0.90 [0.47, 1.73], 0.7443	
RD [95%-CI]; p-value	-0.16 [-0.37, 0.05], 0.1311		0.12 [-0.09, 0.33], 0.2601		-0.02 [-0.17, 0.12], 0.7454	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	34/82 (41.5)	16/42 (38.1)	29/94 (30.9)	9/40 (22.5)	63/176 (35.8)	25/82 (30.5)
RR [95%-CI]; p-value	1.09 [0.68, 1.73], 0.7201		1.37 [0.72, 2.63], 0.3411		1.17 [0.80, 1.72], 0.4103	
OR [95%-CI]; p-value	1.15 [0.54, 2.47], 0.7175		1.54 [0.65, 3.64], 0.3264		1.27 [0.72, 2.23], 0.4024	
RD [95%-CI]; p-value	0.03 [-0.15, 0.22], 0.7161		0.08 [-0.08, 0.24], 0.3050		0.05 [-0.07, 0.18], 0.3948	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.2381		0.8988		0.4003	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	0/30 (0.0)	5/50 (10.0)	4/32 (12.5)	11/109 (10.1)	4/62 (6.5)
RR [95%-CI]; p-value	6.20 [0.36, 107.42], 0.2097		0.80 [0.23, 2.76], 0.7238		1.56 [0.52, 4.70], 0.4258	
OR [95%-CI]; p-value	6.79 [0.37, 125.88], 0.1405		0.78 [0.19, 3.14], 0.7239		1.63 [0.50, 5.35], 0.4185	
RD [95%-CI]; p-value	0.09 [-0.00, 0.17], 0.0612		-0.03 [-0.17, 0.12], 0.7293		0.04 [-0.05, 0.12], 0.3917	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	12/82 (14.6)	6/42 (14.3)	5/94 (5.3)	3/40 (7.5)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	1.02 [0.41, 2.54], 0.9585		0.71 [0.18, 2.83], 0.6262		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	1.03 [0.36, 2.97], 0.9584		0.69 [0.16, 3.05], 0.6259		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	0.00 [-0.13, 0.13], 0.9583		-0.02 [-0.12, 0.07], 0.6472		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1373		0.3747		0.5296	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	2/50 (4.0)	2/32 (6.3)	8/109 (7.3)	4/62 (6.5)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		0.64 [0.09, 4.32], 0.6468		1.14 [0.36, 3.63], 0.8274	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		0.63 [0.08, 4.68], 0.6445		1.15 [0.33, 3.98], 0.8270	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		-0.02 [-0.12, 0.08], 0.6590		0.01 [-0.07, 0.09], 0.8242	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	7/42 (16.7)	9/94 (9.6)	2/40 (5.0)	14/176 (8.0)	9/82 (11.0)
RR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0695		1.91 [0.43, 8.47], 0.3918		0.72 [0.33, 1.61], 0.4276	
OR [95%-CI]; p-value	0.32 [0.10, 1.09], 0.0596		2.01 [0.41, 9.76], 0.3774		0.70 [0.29, 1.69], 0.4278	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.02], 0.0949		0.05 [-0.04, 0.14], 0.3191		-0.03 [-0.11, 0.05], 0.4512	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1800		0.1278		0.1434	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	8/59 (13.6)	9/30 (30.0)	11/50 (22.0)	6/32 (18.8)	19/109 (17.4)	15/62 (24.2)
RR [95%-CI]; p-value	0.45 [0.19, 1.05], 0.0654		1.17 [0.48, 2.86], 0.7249		0.72 [0.40, 1.31], 0.2849	
OR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0622		1.22 [0.40, 3.71], 0.7232		0.66 [0.31, 1.42], 0.2868	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0829		0.03 [-0.14, 0.21], 0.7195		-0.07 [-0.20, 0.06], 0.3012	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	20/82 (24.4)	11/42 (26.2)	15/94 (16.0)	1/40 (2.5)	35/176 (19.9)	12/82 (14.6)
RR [95%-CI]; p-value	0.93 [0.49, 1.76], 0.8260		6.38 [0.87, 46.70], 0.0679		1.36 [0.75, 2.48], 0.3173	
OR [95%-CI]; p-value	0.91 [0.39, 2.13], 0.8266		7.41 [0.94, 58.12], 0.0279		1.45 [0.71, 2.96], 0.3088	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.14], 0.8278		0.13 [0.05, 0.22], 0.0029		0.05 [-0.04, 0.15], 0.2865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9734		0.7041		0.8371	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	9/59 (15.3)	7/30 (23.3)	5/50 (10.0)	5/32 (15.6)	14/109 (12.8)	12/62 (19.4)
RR [95%-CI]; p-value	0.65 [0.27, 1.58], 0.3463		0.64 [0.20, 2.04], 0.4498		0.66 [0.33, 1.34], 0.2544	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3481		0.60 [0.16, 2.26], 0.4477		0.61 [0.26, 1.43], 0.2543	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3709		-0.06 [-0.21, 0.09], 0.4647		-0.07 [-0.18, 0.05], 0.2741	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	8/42 (19.0)	12/94 (12.8)	6/40 (15.0)	22/176 (12.5)	14/82 (17.1)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3050		0.85 [0.34, 2.11], 0.7276		0.73 [0.40, 1.36], 0.3217	
OR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3053		0.83 [0.29, 2.39], 0.7286		0.69 [0.33, 1.44], 0.3236	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3314		-0.02 [-0.15, 0.11], 0.7355		-0.05 [-0.14, 0.05], 0.3453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1273		0.6134		0.1585	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	16/59 (27.1)	12/30 (40.0)	13/50 (26.0)	9/32 (28.1)	29/109 (26.6)	21/62 (33.9)
RR [95%-CI]; p-value	0.68 [0.37, 1.24], 0.2086		0.92 [0.45, 1.91], 0.8318		0.79 [0.49, 1.25], 0.3110	
OR [95%-CI]; p-value	0.56 [0.22, 1.41], 0.2161		0.90 [0.33, 2.43], 0.8322		0.71 [0.36, 1.39], 0.3153	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.08], 0.2266		-0.02 [-0.22, 0.18], 0.8331		-0.07 [-0.22, 0.07], 0.3230	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	22/82 (26.8)	8/42 (19.0)	20/94 (21.3)	7/40 (17.5)	42/176 (23.9)	15/82 (18.3)
RR [95%-CI]; p-value	1.41 [0.69, 2.89], 0.3502		1.22 [0.56, 2.64], 0.6221		1.30 [0.77, 2.21], 0.3238	
OR [95%-CI]; p-value	1.56 [0.63, 3.88], 0.3383		1.27 [0.49, 3.31], 0.6180		1.40 [0.72, 2.70], 0.3152	
RD [95%-CI]; p-value	0.08 [-0.07, 0.23], 0.3177		0.04 [-0.11, 0.18], 0.6070		0.06 [-0.05, 0.16], 0.2971	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8356		0.9298		0.9637	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	3/50 (6.0)	1/32 (3.1)	9/109 (8.3)	3/62 (4.8)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		1.92 [0.21, 17.66], 0.5645		1.71 [0.48, 6.07], 0.4091	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		1.98 [0.20, 19.90], 0.5555		1.77 [0.46, 6.80], 0.4002	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		0.03 [-0.06, 0.12], 0.5279		0.03 [-0.04, 0.11], 0.3673	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	11/82 (13.4)	3/42 (7.1)	8/94 (8.5)	2/40 (5.0)	19/176 (10.8)	5/82 (6.1)
RR [95%-CI]; p-value	1.88 [0.55, 6.37], 0.3118		1.70 [0.38, 7.66], 0.4884		1.77 [0.68, 4.58], 0.2384	
OR [95%-CI]; p-value	2.01 [0.53, 7.65], 0.2963		1.77 [0.36, 8.72], 0.4792		1.86 [0.67, 5.18], 0.2264	
RD [95%-CI]; p-value	0.06 [-0.04, 0.17], 0.2518		0.04 [-0.05, 0.12], 0.4343		0.05 [-0.02, 0.12], 0.1831	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1325		0.6030		0.3912	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	10/59 (16.9)	3/30 (10.0)	5/50 (10.0)	4/32 (12.5)	15/109 (13.8)	7/62 (11.3)
RR [95%-CI]; p-value	1.69 [0.50, 5.70], 0.3939		0.80 [0.23, 2.76], 0.7238		1.22 [0.53, 2.83], 0.6447	
OR [95%-CI]; p-value	1.84 [0.47, 7.25], 0.3802		0.78 [0.19, 3.14], 0.7239		1.25 [0.48, 3.26], 0.6427	
RD [95%-CI]; p-value	0.07 [-0.07, 0.21], 0.3437		-0.03 [-0.17, 0.12], 0.7293		0.02 [-0.08, 0.13], 0.6346	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	7/82 (8.5)	7/42 (16.7)	9/94 (9.6)	3/40 (7.5)	16/176 (9.1)	10/82 (12.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.36], 0.1806		1.28 [0.36, 4.47], 0.7025		0.75 [0.35, 1.57], 0.4398	
OR [95%-CI]; p-value	0.47 [0.15, 1.43], 0.1758		1.31 [0.33, 5.10], 0.7004		0.72 [0.31, 1.66], 0.4406	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2128		0.02 [-0.08, 0.12], 0.6873		-0.03 [-0.11, 0.05], 0.4613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6345		0.6370		0.4541	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	11/59 (18.6)	7/30 (23.3)	9/50 (18.0)	5/32 (15.6)	20/109 (18.3)	12/62 (19.4)
RR [95%-CI]; p-value	0.80 [0.35, 1.85], 0.6004		1.15 [0.42, 3.13], 0.7813		0.95 [0.50, 1.81], 0.8710	
OR [95%-CI]; p-value	0.75 [0.26, 2.20], 0.6026		1.19 [0.36, 3.92], 0.7804		0.94 [0.42, 2.07], 0.8712	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.6117		0.02 [-0.14, 0.19], 0.7776		-0.01 [-0.13, 0.11], 0.8719	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	17/82 (20.7)	14/42 (33.3)	16/94 (17.0)	8/40 (20.0)	33/176 (18.8)	22/82 (26.8)
RR [95%-CI]; p-value	0.62 [0.34, 1.14], 0.1219		0.85 [0.40, 1.83], 0.6790		0.70 [0.44, 1.12], 0.1364	
OR [95%-CI]; p-value	0.52 [0.23, 1.21], 0.1251		0.82 [0.32, 2.11], 0.6807		0.63 [0.34, 1.17], 0.1401	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1401		-0.03 [-0.18, 0.12], 0.6880		-0.08 [-0.19, 0.03], 0.1570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2393		0.9821		0.4212	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	9/30 (30.0)	6/50 (12.0)	5/32 (15.6)	12/109 (11.0)	14/62 (22.6)
RR [95%-CI]; p-value	0.34 [0.13, 0.86], 0.0233		0.77 [0.26, 2.31], 0.6383		0.49 [0.24, 0.99], 0.0459	
OR [95%-CI]; p-value	0.26 [0.08, 0.83], 0.0182		0.74 [0.20, 2.65], 0.6385		0.42 [0.18, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.20 [-0.38, -0.02], 0.0320		-0.04 [-0.19, 0.12], 0.6461		-0.12 [-0.24, 0.00], 0.0577	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	18/82 (22.0)	14/42 (33.3)	16/94 (17.0)	9/40 (22.5)	34/176 (19.3)	23/82 (28.0)
RR [95%-CI]; p-value	0.66 [0.36, 1.19], 0.1661		0.76 [0.37, 1.57], 0.4525		0.69 [0.43, 1.09], 0.1119	
OR [95%-CI]; p-value	0.56 [0.25, 1.29], 0.1704		0.71 [0.28, 1.77], 0.4563		0.61 [0.33, 1.13], 0.1155	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.05], 0.1852		-0.05 [-0.20, 0.10], 0.4742		-0.09 [-0.20, 0.03], 0.1313	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.8439		0.5300		0.7790	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	6/30 (20.0)	8/50 (16.0)	5/32 (15.6)	14/109 (12.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.51 [0.18, 1.44], 0.2036		1.02 [0.37, 2.86], 0.9638		0.72 [0.35, 1.50], 0.3828	
OR [95%-CI]; p-value	0.45 [0.13, 1.55], 0.1993		1.03 [0.30, 3.48], 0.9638		0.68 [0.29, 1.61], 0.3835	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2360		0.00 [-0.16, 0.17], 0.9637		-0.05 [-0.16, 0.06], 0.3996	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	7/42 (16.7)	12/94 (12.8)	3/40 (7.5)	18/176 (10.2)	10/82 (12.2)
RR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1155		1.70 [0.51, 5.71], 0.3889		0.84 [0.41, 1.74], 0.6353	
OR [95%-CI]; p-value	0.39 [0.12, 1.26], 0.1077		1.80 [0.48, 6.78], 0.3763		0.82 [0.36, 1.87], 0.6361	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1459		0.05 [-0.05, 0.16], 0.3297		-0.02 [-0.10, 0.06], 0.6453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8647		0.9177		0.7386	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	3/30 (10.0)	6/50 (12.0)	3/32 (9.4)	11/109 (10.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.85 [0.22, 3.31], 0.8118		1.28 [0.34, 4.76], 0.7125		1.04 [0.41, 2.68], 0.9307	
OR [95%-CI]; p-value	0.83 [0.19, 3.75], 0.8120		1.32 [0.31, 5.69], 0.7107		1.05 [0.37, 2.99], 0.9306	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8164		0.03 [-0.11, 0.16], 0.7038		0.00 [-0.09, 0.10], 0.9303	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	13/82 (15.9)	9/42 (21.4)	11/94 (11.7)	4/40 (10.0)	24/176 (13.6)	13/82 (15.9)
RR [95%-CI]; p-value	0.74 [0.34, 1.59], 0.4396		1.17 [0.40, 3.46], 0.7760		0.86 [0.46, 1.60], 0.6350	
OR [95%-CI]; p-value	0.69 [0.27, 1.78], 0.4418		1.19 [0.36, 4.00], 0.7749		0.84 [0.40, 1.74], 0.6361	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.09], 0.4577		0.02 [-0.10, 0.13], 0.7687		-0.02 [-0.12, 0.07], 0.6436	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9936		0.7839		0.6691	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	4/59 (6.8)	4/30 (13.3)	3/50 (6.0)	2/32 (6.3)	7/109 (6.4)	6/62 (9.7)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3132		0.96 [0.17, 5.43], 0.9632		0.66 [0.23, 1.89], 0.4418	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3069		0.96 [0.15, 6.07], 0.9632		0.64 [0.21, 2.00], 0.4400	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3503		-0.00 [-0.11, 0.10], 0.9633		-0.03 [-0.12, 0.05], 0.4623	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	5/42 (11.9)	12/94 (12.8)	4/40 (10.0)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	0.51 [0.16, 1.67], 0.2675		1.28 [0.44, 3.72], 0.6545		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	0.48 [0.13, 1.76], 0.2610		1.32 [0.40, 4.36], 0.6514		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.3043		0.03 [-0.09, 0.14], 0.6370		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.0990		0.9469		0.2086	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	6/30 (20.0)	5/50 (10.0)	4/32 (12.5)	10/109 (9.2)	10/62 (16.1)
RR [95%-CI]; p-value	0.42 [0.14, 1.28], 0.1269		0.80 [0.23, 2.76], 0.7238		0.57 [0.25, 1.29], 0.1770	
OR [95%-CI]; p-value	0.37 [0.10, 1.33], 0.1184		0.78 [0.19, 3.14], 0.7239		0.53 [0.21, 1.34], 0.1737	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1575		-0.03 [-0.17, 0.12], 0.7293		-0.07 [-0.18, 0.04], 0.2001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	3/42 (7.1)	6/94 (6.4)	3/40 (7.5)	16/176 (9.1)	6/82 (7.3)
RR [95%-CI]; p-value	1.71 [0.50, 5.87], 0.3961		0.85 [0.22, 3.24], 0.8129		1.24 [0.50, 3.06], 0.6368	
OR [95%-CI]; p-value	1.81 [0.47, 6.95], 0.3848		0.84 [0.20, 3.54], 0.8131		1.27 [0.48, 3.37], 0.6348	
RD [95%-CI]; p-value	0.05 [-0.05, 0.16], 0.3469		-0.01 [-0.11, 0.08], 0.8185		0.02 [-0.05, 0.09], 0.6223	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.3.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3014		0.8476		0.5548	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	7/30 (23.3)	3/50 (6.0)	0/32 (0.0)	5/109 (4.6)	7/62 (11.3)
RR [95%-CI]; p-value	0.15 [0.03, 0.66], 0.0122		3.90 [0.20, 75.35], 0.3677		0.41 [0.13, 1.23], 0.1100	
OR [95%-CI]; p-value	0.12 [0.02, 0.60], 0.0032		4.09 [0.20, 84.33], 0.3259		0.38 [0.11, 1.25], 0.0990	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0135		0.04 [-0.03, 0.12], 0.2638		-0.07 [-0.16, 0.02], 0.1356	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	4/82 (4.9)	5/42 (11.9)	3/94 (3.2)	0/40 (0.0)	7/176 (4.0)	5/82 (6.1)
RR [95%-CI]; p-value	0.41 [0.12, 1.45], 0.1656		2.59 [0.13, 50.45], 0.5310		0.65 [0.21, 1.99], 0.4535	
OR [95%-CI]; p-value	0.38 [0.10, 1.50], 0.1535		2.64 [0.13, 53.88], 0.5131		0.64 [0.20, 2.07], 0.4514	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2042		0.02 [-0.03, 0.07], 0.4355		-0.02 [-0.08, 0.04], 0.4834	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_3_m_pt_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.3.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2547		0.4086		0.2552	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	4/30 (13.3)	2/50 (4.0)	2/32 (6.3)	3/109 (2.8)	6/62 (9.7)
RR [95%-CI]; p-value	0.13 [0.01, 1.09], 0.0597		0.64 [0.09, 4.32], 0.6468		0.28 [0.07, 1.10], 0.0680	
OR [95%-CI]; p-value	0.11 [0.01, 1.05], 0.0242		0.63 [0.08, 4.68], 0.6445		0.26 [0.06, 1.10], 0.0512	
RD [95%-CI]; p-value	-0.12 [-0.24, 0.01], 0.0703		-0.02 [-0.12, 0.08], 0.6590		-0.07 [-0.15, 0.01], 0.0887	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	6/42 (14.3)	5/94 (5.3)	1/40 (2.5)	11/176 (6.3)	7/82 (8.5)
RR [95%-CI]; p-value	0.51 [0.18, 1.49], 0.2198		2.13 [0.26, 17.64], 0.4841		0.73 [0.29, 1.82], 0.5022	
OR [95%-CI]; p-value	0.47 [0.14, 1.57], 0.2142		2.19 [0.25, 19.38], 0.4702		0.71 [0.27, 1.91], 0.5020	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2547		0.03 [-0.04, 0.09], 0.4048		-0.02 [-0.09, 0.05], 0.5236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_3_m_pt_ae10pct_age.sas using SAS 9.4

Table 12.4.8.1.1.s1
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2654		0.5725		0.1119	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	0/59 (0.0)	1/30 (3.3)	3/50 (6.0)	3/32 (9.4)	3/109 (2.8)	4/62 (6.5)
RR [95%-CI]; p-value	0.25 [0.01, 7.30], 0.4224		0.64 [0.14, 2.98], 0.5694		0.43 [0.10, 1.84], 0.2541	
OR [95%-CI]; p-value	0.25 [0.01, 7.54], 0.3858		0.62 [0.12, 3.26], 0.5670		0.41 [0.09, 1.90], 0.2405	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.04], 0.4743		-0.03 [-0.15, 0.09], 0.5832		-0.04 [-0.11, 0.03], 0.2894	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	8/82 (9.8)	2/42 (4.8)	2/94 (2.1)	0/40 (0.0)	10/176 (5.7)	2/82 (2.4)
RR [95%-CI]; p-value	2.05 [0.46, 9.22], 0.3500		1.72 [0.08, 37.39], 0.7288		2.33 [0.52, 10.39], 0.2677	
OR [95%-CI]; p-value	2.16 [0.44, 10.67], 0.3337		1.74 [0.08, 39.43], 0.7250		2.41 [0.52, 11.26], 0.2494	
RD [95%-CI]; p-value	0.05 [-0.04, 0.14], 0.2818		0.01 [-0.04, 0.05], 0.6960		0.03 [-0.02, 0.08], 0.1836	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_8_1_1_m_soc_sae5pct_age.sas using SAS 9.4

Table 12.4.8.1.2.s1
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_8_1_2_m_pt_sae5pct_age.sas using SAS 9.4

Table 12.4.5.1.1.s1
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_5_1_1_m_soc_aeg35pct_age.sas using SAS 9.4

Table 12.4.5.1.2.s1
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_5_1_2_m_pt_aeg35pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1373		0.3747		0.5296	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	2/50 (4.0)	2/32 (6.3)	8/109 (7.3)	4/62 (6.5)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		0.64 [0.09, 4.32], 0.6468		1.14 [0.36, 3.63], 0.8274	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		0.63 [0.08, 4.68], 0.6445		1.15 [0.33, 3.98], 0.8270	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		-0.02 [-0.12, 0.08], 0.6590		0.01 [-0.07, 0.09], 0.8242	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	7/42 (16.7)	9/94 (9.6)	2/40 (5.0)	14/176 (8.0)	9/82 (11.0)
RR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0695		1.91 [0.43, 8.47], 0.3918		0.72 [0.33, 1.61], 0.4276	
OR [95%-CI]; p-value	0.32 [0.10, 1.09], 0.0596		2.01 [0.41, 9.76], 0.3774		0.70 [0.29, 1.69], 0.4278	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.02], 0.0949		0.05 [-0.04, 0.14], 0.3191		-0.03 [-0.11, 0.05], 0.4512	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1800		0.1278		0.1434	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	8/59 (13.6)	9/30 (30.0)	11/50 (22.0)	6/32 (18.8)	19/109 (17.4)	15/62 (24.2)
RR [95%-CI]; p-value	0.45 [0.19, 1.05], 0.0654		1.17 [0.48, 2.86], 0.7249		0.72 [0.40, 1.31], 0.2849	
OR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0622		1.22 [0.40, 3.71], 0.7232		0.66 [0.31, 1.42], 0.2868	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0829		0.03 [-0.14, 0.21], 0.7195		-0.07 [-0.20, 0.06], 0.3012	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	20/82 (24.4)	11/42 (26.2)	15/94 (16.0)	1/40 (2.5)	35/176 (19.9)	12/82 (14.6)
RR [95%-CI]; p-value	0.93 [0.49, 1.76], 0.8260		6.38 [0.87, 46.70], 0.0679		1.36 [0.75, 2.48], 0.3173	
OR [95%-CI]; p-value	0.91 [0.39, 2.13], 0.8266		7.41 [0.94, 58.12], 0.0279		1.45 [0.71, 2.96], 0.3088	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.14], 0.8278		0.13 [0.05, 0.22], 0.0029		0.05 [-0.04, 0.15], 0.2865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9734		0.7041		0.8371	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	9/59 (15.3)	7/30 (23.3)	5/50 (10.0)	5/32 (15.6)	14/109 (12.8)	12/62 (19.4)
RR [95%-CI]; p-value	0.65 [0.27, 1.58], 0.3463		0.64 [0.20, 2.04], 0.4498		0.66 [0.33, 1.34], 0.2544	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3481		0.60 [0.16, 2.26], 0.4477		0.61 [0.26, 1.43], 0.2543	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3709		-0.06 [-0.21, 0.09], 0.4647		-0.07 [-0.18, 0.05], 0.2741	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	8/42 (19.0)	12/94 (12.8)	6/40 (15.0)	22/176 (12.5)	14/82 (17.1)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3050		0.85 [0.34, 2.11], 0.7276		0.73 [0.40, 1.36], 0.3217	
OR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3053		0.83 [0.29, 2.39], 0.7286		0.69 [0.33, 1.44], 0.3236	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3314		-0.02 [-0.15, 0.11], 0.7355		-0.05 [-0.14, 0.05], 0.3453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1273		0.6134		0.1585	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	16/59 (27.1)	12/30 (40.0)	13/50 (26.0)	9/32 (28.1)	29/109 (26.6)	21/62 (33.9)
RR [95%-CI]; p-value	0.68 [0.37, 1.24], 0.2086		0.92 [0.45, 1.91], 0.8318		0.79 [0.49, 1.25], 0.3110	
OR [95%-CI]; p-value	0.56 [0.22, 1.41], 0.2161		0.90 [0.33, 2.43], 0.8322		0.71 [0.36, 1.39], 0.3153	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.08], 0.2266		-0.02 [-0.22, 0.18], 0.8331		-0.07 [-0.22, 0.07], 0.3230	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	22/82 (26.8)	8/42 (19.0)	20/94 (21.3)	7/40 (17.5)	42/176 (23.9)	15/82 (18.3)
RR [95%-CI]; p-value	1.41 [0.69, 2.89], 0.3502		1.22 [0.56, 2.64], 0.6221		1.30 [0.77, 2.21], 0.3238	
OR [95%-CI]; p-value	1.56 [0.63, 3.88], 0.3383		1.27 [0.49, 3.31], 0.6180		1.40 [0.72, 2.70], 0.3152	
RD [95%-CI]; p-value	0.08 [-0.07, 0.23], 0.3177		0.04 [-0.11, 0.18], 0.6070		0.06 [-0.05, 0.16], 0.2971	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8356		0.9298		0.9637	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	3/50 (6.0)	1/32 (3.1)	9/109 (8.3)	3/62 (4.8)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		1.92 [0.21, 17.66], 0.5645		1.71 [0.48, 6.07], 0.4091	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		1.98 [0.20, 19.90], 0.5555		1.77 [0.46, 6.80], 0.4002	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		0.03 [-0.06, 0.12], 0.5279		0.03 [-0.04, 0.11], 0.3673	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	11/82 (13.4)	3/42 (7.1)	8/94 (8.5)	2/40 (5.0)	19/176 (10.8)	5/82 (6.1)
RR [95%-CI]; p-value	1.88 [0.55, 6.37], 0.3118		1.70 [0.38, 7.66], 0.4884		1.77 [0.68, 4.58], 0.2384	
OR [95%-CI]; p-value	2.01 [0.53, 7.65], 0.2963		1.77 [0.36, 8.72], 0.4792		1.86 [0.67, 5.18], 0.2264	
RD [95%-CI]; p-value	0.06 [-0.04, 0.17], 0.2518		0.04 [-0.05, 0.12], 0.4343		0.05 [-0.02, 0.12], 0.1831	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1325		0.6030		0.3912	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	10/59 (16.9)	3/30 (10.0)	5/50 (10.0)	4/32 (12.5)	15/109 (13.8)	7/62 (11.3)
RR [95%-CI]; p-value	1.69 [0.50, 5.70], 0.3939		0.80 [0.23, 2.76], 0.7238		1.22 [0.53, 2.83], 0.6447	
OR [95%-CI]; p-value	1.84 [0.47, 7.25], 0.3802		0.78 [0.19, 3.14], 0.7239		1.25 [0.48, 3.26], 0.6427	
RD [95%-CI]; p-value	0.07 [-0.07, 0.21], 0.3437		-0.03 [-0.17, 0.12], 0.7293		0.02 [-0.08, 0.13], 0.6346	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	7/82 (8.5)	7/42 (16.7)	9/94 (9.6)	3/40 (7.5)	16/176 (9.1)	10/82 (12.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.36], 0.1806		1.28 [0.36, 4.47], 0.7025		0.75 [0.35, 1.57], 0.4398	
OR [95%-CI]; p-value	0.47 [0.15, 1.43], 0.1758		1.31 [0.33, 5.10], 0.7004		0.72 [0.31, 1.66], 0.4406	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2128		0.02 [-0.08, 0.12], 0.6873		-0.03 [-0.11, 0.05], 0.4613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6345		0.6370		0.4541	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	11/59 (18.6)	7/30 (23.3)	9/50 (18.0)	5/32 (15.6)	20/109 (18.3)	12/62 (19.4)
RR [95%-CI]; p-value	0.80 [0.35, 1.85], 0.6004		1.15 [0.42, 3.13], 0.7813		0.95 [0.50, 1.81], 0.8710	
OR [95%-CI]; p-value	0.75 [0.26, 2.20], 0.6026		1.19 [0.36, 3.92], 0.7804		0.94 [0.42, 2.07], 0.8712	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.6117		0.02 [-0.14, 0.19], 0.7776		-0.01 [-0.13, 0.11], 0.8719	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	17/82 (20.7)	14/42 (33.3)	16/94 (17.0)	8/40 (20.0)	33/176 (18.8)	22/82 (26.8)
RR [95%-CI]; p-value	0.62 [0.34, 1.14], 0.1219		0.85 [0.40, 1.83], 0.6790		0.70 [0.44, 1.12], 0.1364	
OR [95%-CI]; p-value	0.52 [0.23, 1.21], 0.1251		0.82 [0.32, 2.11], 0.6807		0.63 [0.34, 1.17], 0.1401	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1401		-0.03 [-0.18, 0.12], 0.6880		-0.08 [-0.19, 0.03], 0.1570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2393		0.9821		0.4212	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	9/30 (30.0)	6/50 (12.0)	5/32 (15.6)	12/109 (11.0)	14/62 (22.6)
RR [95%-CI]; p-value	0.34 [0.13, 0.86], 0.0233		0.77 [0.26, 2.31], 0.6383		0.49 [0.24, 0.99], 0.0459	
OR [95%-CI]; p-value	0.26 [0.08, 0.83], 0.0182		0.74 [0.20, 2.65], 0.6385		0.42 [0.18, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.20 [-0.38, -0.02], 0.0320		-0.04 [-0.19, 0.12], 0.6461		-0.12 [-0.24, 0.00], 0.0577	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	18/82 (22.0)	14/42 (33.3)	16/94 (17.0)	9/40 (22.5)	34/176 (19.3)	23/82 (28.0)
RR [95%-CI]; p-value	0.66 [0.36, 1.19], 0.1661		0.76 [0.37, 1.57], 0.4525		0.69 [0.43, 1.09], 0.1119	
OR [95%-CI]; p-value	0.56 [0.25, 1.29], 0.1704		0.71 [0.28, 1.77], 0.4563		0.61 [0.33, 1.13], 0.1155	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.05], 0.1852		-0.05 [-0.20, 0.10], 0.4742		-0.09 [-0.20, 0.03], 0.1313	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.8439		0.5300		0.7790	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	6/30 (20.0)	8/50 (16.0)	5/32 (15.6)	14/109 (12.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.51 [0.18, 1.44], 0.2036		1.02 [0.37, 2.86], 0.9638		0.72 [0.35, 1.50], 0.3828	
OR [95%-CI]; p-value	0.45 [0.13, 1.55], 0.1993		1.03 [0.30, 3.48], 0.9638		0.68 [0.29, 1.61], 0.3835	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2360		0.00 [-0.16, 0.17], 0.9637		-0.05 [-0.16, 0.06], 0.3996	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	7/42 (16.7)	12/94 (12.8)	3/40 (7.5)	18/176 (10.2)	10/82 (12.2)
RR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1155		1.70 [0.51, 5.71], 0.3889		0.84 [0.41, 1.74], 0.6353	
OR [95%-CI]; p-value	0.39 [0.12, 1.26], 0.1077		1.80 [0.48, 6.78], 0.3763		0.82 [0.36, 1.87], 0.6361	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1459		0.05 [-0.05, 0.16], 0.3297		-0.02 [-0.10, 0.06], 0.6453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.2069		0.5396		0.6918	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	1/30 (3.3)	4/50 (8.0)	4/32 (12.5)	10/109 (9.2)	5/62 (8.1)
RR [95%-CI]; p-value	3.05 [0.38, 24.20], 0.2911		0.64 [0.17, 2.38], 0.5053		1.14 [0.41, 3.18], 0.8057	
OR [95%-CI]; p-value	3.28 [0.38, 28.61], 0.2574		0.61 [0.14, 2.63], 0.5029		1.15 [0.38, 3.54], 0.8052	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1819		-0.05 [-0.18, 0.09], 0.5199		0.01 [-0.08, 0.10], 0.8021	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	4/42 (9.5)	8/94 (8.5)	3/40 (7.5)	13/176 (7.4)	7/82 (8.5)
RR [95%-CI]; p-value	0.64 [0.18, 2.26], 0.4883		1.13 [0.32, 4.06], 0.8458		0.87 [0.36, 2.09], 0.7474	
OR [95%-CI]; p-value	0.62 [0.16, 2.43], 0.4864		1.15 [0.29, 4.57], 0.8454		0.85 [0.33, 2.23], 0.7477	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5135		0.01 [-0.09, 0.11], 0.8418		-0.01 [-0.08, 0.06], 0.7534	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8647		0.9177		0.7386	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	3/30 (10.0)	6/50 (12.0)	3/32 (9.4)	11/109 (10.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.85 [0.22, 3.31], 0.8118		1.28 [0.34, 4.76], 0.7125		1.04 [0.41, 2.68], 0.9307	
OR [95%-CI]; p-value	0.83 [0.19, 3.75], 0.8120		1.32 [0.31, 5.69], 0.7107		1.05 [0.37, 2.99], 0.9306	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8164		0.03 [-0.11, 0.16], 0.7038		0.00 [-0.09, 0.10], 0.9303	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	13/82 (15.9)	9/42 (21.4)	11/94 (11.7)	4/40 (10.0)	24/176 (13.6)	13/82 (15.9)
RR [95%-CI]; p-value	0.74 [0.34, 1.59], 0.4396		1.17 [0.40, 3.46], 0.7760		0.86 [0.46, 1.60], 0.6350	
OR [95%-CI]; p-value	0.69 [0.27, 1.78], 0.4418		1.19 [0.36, 4.00], 0.7749		0.84 [0.40, 1.74], 0.6361	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.09], 0.4577		0.02 [-0.10, 0.13], 0.7687		-0.02 [-0.12, 0.07], 0.6436	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9936		0.7839		0.6691	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	4/59 (6.8)	4/30 (13.3)	3/50 (6.0)	2/32 (6.3)	7/109 (6.4)	6/62 (9.7)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3132		0.96 [0.17, 5.43], 0.9632		0.66 [0.23, 1.89], 0.4418	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3069		0.96 [0.15, 6.07], 0.9632		0.64 [0.21, 2.00], 0.4400	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3503		-0.00 [-0.11, 0.10], 0.9633		-0.03 [-0.12, 0.05], 0.4623	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	5/42 (11.9)	12/94 (12.8)	4/40 (10.0)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	0.51 [0.16, 1.67], 0.2675		1.28 [0.44, 3.72], 0.6545		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	0.48 [0.13, 1.76], 0.2610		1.32 [0.40, 4.36], 0.6514		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.3043		0.03 [-0.09, 0.14], 0.6370		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.0990		0.9469		0.2086	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	6/30 (20.0)	5/50 (10.0)	4/32 (12.5)	10/109 (9.2)	10/62 (16.1)
RR [95%-CI]; p-value	0.42 [0.14, 1.28], 0.1269		0.80 [0.23, 2.76], 0.7238		0.57 [0.25, 1.29], 0.1770	
OR [95%-CI]; p-value	0.37 [0.10, 1.33], 0.1184		0.78 [0.19, 3.14], 0.7239		0.53 [0.21, 1.34], 0.1737	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1575		-0.03 [-0.17, 0.12], 0.7293		-0.07 [-0.18, 0.04], 0.2001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	3/42 (7.1)	6/94 (6.4)	3/40 (7.5)	16/176 (9.1)	6/82 (7.3)
RR [95%-CI]; p-value	1.71 [0.50, 5.87], 0.3961		0.85 [0.22, 3.24], 0.8129		1.24 [0.50, 3.06], 0.6368	
OR [95%-CI]; p-value	1.81 [0.47, 6.95], 0.3848		0.84 [0.20, 3.54], 0.8131		1.27 [0.48, 3.37], 0.6348	
RD [95%-CI]; p-value	0.05 [-0.05, 0.16], 0.3469		-0.01 [-0.11, 0.08], 0.8185		0.02 [-0.05, 0.09], 0.6223	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.4.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3014		0.8476		0.5548	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	7/30 (23.3)	3/50 (6.0)	0/32 (0.0)	5/109 (4.6)	7/62 (11.3)
RR [95%-CI]; p-value	0.15 [0.03, 0.66], 0.0122		3.90 [0.20, 75.35], 0.3677		0.41 [0.13, 1.23], 0.1100	
OR [95%-CI]; p-value	0.12 [0.02, 0.60], 0.0032		4.09 [0.20, 84.33], 0.3259		0.38 [0.11, 1.25], 0.0990	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0135		0.04 [-0.03, 0.12], 0.2638		-0.07 [-0.16, 0.02], 0.1356	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	4/82 (4.9)	5/42 (11.9)	3/94 (3.2)	0/40 (0.0)	7/176 (4.0)	5/82 (6.1)
RR [95%-CI]; p-value	0.41 [0.12, 1.45], 0.1656		2.59 [0.13, 50.45], 0.5310		0.65 [0.21, 1.99], 0.4535	
OR [95%-CI]; p-value	0.38 [0.10, 1.50], 0.1535		2.64 [0.13, 53.88], 0.5131		0.64 [0.20, 2.07], 0.4514	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2042		0.02 [-0.03, 0.07], 0.4355		-0.02 [-0.08, 0.04], 0.4834	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_4_m_pt_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.4.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2547		0.4086		0.2552	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	4/30 (13.3)	2/50 (4.0)	2/32 (6.3)	3/109 (2.8)	6/62 (9.7)
RR [95%-CI]; p-value	0.13 [0.01, 1.09], 0.0597		0.64 [0.09, 4.32], 0.6468		0.28 [0.07, 1.10], 0.0680	
OR [95%-CI]; p-value	0.11 [0.01, 1.05], 0.0242		0.63 [0.08, 4.68], 0.6445		0.26 [0.06, 1.10], 0.0512	
RD [95%-CI]; p-value	-0.12 [-0.24, 0.01], 0.0703		-0.02 [-0.12, 0.08], 0.6590		-0.07 [-0.15, 0.01], 0.0887	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	6/42 (14.3)	5/94 (5.3)	1/40 (2.5)	11/176 (6.3)	7/82 (8.5)
RR [95%-CI]; p-value	0.51 [0.18, 1.49], 0.2198		2.13 [0.26, 17.64], 0.4841		0.73 [0.29, 1.82], 0.5022	
OR [95%-CI]; p-value	0.47 [0.14, 1.57], 0.2142		2.19 [0.25, 19.38], 0.4702		0.71 [0.27, 1.91], 0.5020	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2547		0.03 [-0.04, 0.09], 0.4048		-0.02 [-0.09, 0.05], 0.5236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_4_m_pt_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.4.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.1524		0.7916		0.2093	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	4/59 (6.8)	4/30 (13.3)	4/50 (8.0)	4/32 (12.5)	8/109 (7.3)	8/62 (12.9)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3132		0.64 [0.17, 2.38], 0.5053		0.57 [0.22, 1.44], 0.2339	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3069		0.61 [0.14, 2.63], 0.5029		0.53 [0.19, 1.50], 0.2297	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3503		-0.05 [-0.18, 0.09], 0.5199		-0.06 [-0.15, 0.04], 0.2597	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	1/42 (2.4)	4/94 (4.3)	2/40 (5.0)	10/176 (5.7)	3/82 (3.7)
RR [95%-CI]; p-value	3.07 [0.38, 24.70], 0.2910		0.85 [0.16, 4.46], 0.8487		1.55 [0.44, 5.49], 0.4946	
OR [95%-CI]; p-value	3.24 [0.38, 27.81], 0.2597		0.84 [0.15, 4.81], 0.8487		1.59 [0.42, 5.92], 0.4891	
RD [95%-CI]; p-value	0.05 [-0.02, 0.12], 0.1840		-0.01 [-0.09, 0.07], 0.8533		0.02 [-0.03, 0.07], 0.4553	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_4_m_pt_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.4410		0.5662		0.9097	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	7/59 (11.9)	0/30 (0.0)	3/50 (6.0)	4/32 (12.5)	10/109 (9.2)	4/62 (6.5)
RR [95%-CI]; p-value	7.24 [0.42, 123.33], 0.1713		0.48 [0.11, 2.01], 0.3143		1.42 [0.47, 4.34], 0.5367	
OR [95%-CI]; p-value	8.08 [0.44, 147.39], 0.0980		0.45 [0.09, 2.14], 0.3042		1.46 [0.44, 4.88], 0.5324	
RD [95%-CI]; p-value	0.10 [0.01, 0.20], 0.0330		-0.07 [-0.20, 0.07], 0.3350		0.03 [-0.05, 0.11], 0.5137	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	8/82 (9.8)	2/42 (4.8)	6/94 (6.4)	3/40 (7.5)	14/176 (8.0)	5/82 (6.1)
RR [95%-CI]; p-value	2.05 [0.46, 9.22], 0.3500		0.85 [0.22, 3.24], 0.8129		1.30 [0.49, 3.50], 0.5975	
OR [95%-CI]; p-value	2.16 [0.44, 10.67], 0.3337		0.84 [0.20, 3.54], 0.8131		1.33 [0.46, 3.83], 0.5949	
RD [95%-CI]; p-value	0.05 [-0.04, 0.14], 0.2818		-0.01 [-0.11, 0.08], 0.8185		0.02 [-0.05, 0.08], 0.5780	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5811		0.8690		0.5721	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	0/59 (0.0)	0/30 (0.0)	1/50 (2.0)	1/32 (3.1)	1/109 (0.9)	1/62 (1.6)
RR [95%-CI]; p-value	NA		0.64 [0.04, 9.87], 0.7492		0.57 [0.04, 8.94], 0.6880	
OR [95%-CI]; p-value	NA		0.63 [0.04, 10.49], 0.7473		0.56 [0.03, 9.19], 0.6843	
RD [95%-CI]; p-value	NA		-0.01 [-0.08, 0.06], 0.7584		-0.01 [-0.04, 0.03], 0.7058	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	2/82 (2.4)	0/42 (0.0)	0/94 (0.0)	0/40 (0.0)	2/176 (1.1)	0/82 (0.0)
RR [95%-CI]; p-value	2.07 [0.10, 44.96], 0.6423		NA		1.88 [0.09, 41.12], 0.6899	
OR [95%-CI]; p-value	2.10 [0.09, 47.62], 0.6339		NA		1.89 [0.08, 42.27], 0.6847	
RD [95%-CI]; p-value	0.01 [-0.03, 0.06], 0.5949		NA		0.01 [-0.02, 0.03], 0.6503	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.3477		0.5363		0.6094	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	7/59 (11.9)	0/30 (0.0)	2/50 (4.0)	3/32 (9.4)	9/109 (8.3)	3/62 (4.8)
RR [95%-CI]; p-value	7.24 [0.42, 123.33], 0.1713		0.43 [0.08, 2.41], 0.3355		1.71 [0.48, 6.07], 0.4091	
OR [95%-CI]; p-value	8.08 [0.44, 147.39], 0.0980		0.40 [0.06, 2.56], 0.3211		1.77 [0.46, 6.80], 0.4002	
RD [95%-CI]; p-value	0.10 [0.01, 0.20], 0.0330		-0.05 [-0.17, 0.06], 0.3583		0.03 [-0.04, 0.11], 0.3673	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	2/42 (4.8)	6/94 (6.4)	3/40 (7.5)	12/176 (6.8)	5/82 (6.1)
RR [95%-CI]; p-value	1.54 [0.32, 7.29], 0.5886		0.85 [0.22, 3.24], 0.8129		1.12 [0.41, 3.07], 0.8284	
OR [95%-CI]; p-value	1.58 [0.30, 8.18], 0.5836		0.84 [0.20, 3.54], 0.8131		1.13 [0.38, 3.31], 0.8280	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5585		-0.01 [-0.11, 0.08], 0.8185		0.01 [-0.06, 0.07], 0.8248	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.9104		0.6351		0.7874	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	0/30 (0.0)	2/50 (4.0)	0/32 (0.0)	4/109 (3.7)	0/62 (0.0)
RR [95%-CI]; p-value	2.07 [0.10, 44.46], 0.6426		2.60 [0.12, 55.86], 0.5415		4.59 [0.25, 85.35], 0.3071	
OR [95%-CI]; p-value	2.11 [0.09, 48.17], 0.6338		2.67 [0.12, 61.06], 0.5239		4.72 [0.25, 90.86], 0.2578	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.5949		0.02 [-0.04, 0.09], 0.4835		0.03 [-0.01, 0.07], 0.1767	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	1/42 (2.4)	1/94 (1.1)	0/40 (0.0)	6/176 (3.4)	1/82 (1.2)
RR [95%-CI]; p-value	2.56 [0.31, 21.22], 0.3834		0.86 [0.03, 25.18], 0.9311		2.80 [0.34, 22.84], 0.3375	
OR [95%-CI]; p-value	2.66 [0.30, 23.56], 0.3614		0.86 [0.03, 26.16], 0.9311		2.86 [0.34, 24.14], 0.3135	
RD [95%-CI]; p-value	0.04 [-0.03, 0.11], 0.2935		-0.00 [-0.04, 0.04], 0.9330		0.02 [-0.01, 0.06], 0.2309	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7825		0.7742		0.9079	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	5/30 (16.7)	4/50 (8.0)	2/32 (6.3)	10/109 (9.2)	7/62 (11.3)
RR [95%-CI]; p-value	0.61 [0.20, 1.84], 0.3798		1.28 [0.25, 6.59], 0.7678		0.81 [0.33, 2.03], 0.6564	
OR [95%-CI]; p-value	0.57 [0.16, 2.03], 0.3787		1.30 [0.22, 7.57], 0.7666		0.79 [0.29, 2.20], 0.6566	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4085		0.02 [-0.10, 0.13], 0.7608		-0.02 [-0.12, 0.07], 0.6645	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	4/42 (9.5)	9/94 (9.6)	4/40 (10.0)	15/176 (8.5)	8/82 (9.8)
RR [95%-CI]; p-value	0.77 [0.23, 2.57], 0.6692		0.96 [0.31, 2.93], 0.9392		0.87 [0.39, 1.98], 0.7458	
OR [95%-CI]; p-value	0.75 [0.20, 2.82], 0.6693		0.95 [0.28, 3.29], 0.9393		0.86 [0.35, 2.12], 0.7462	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.08], 0.6809		-0.00 [-0.11, 0.11], 0.9398		-0.01 [-0.09, 0.06], 0.7515	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5811		0.5724		0.9141	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	0/59 (0.0)	0/30 (0.0)	2/50 (4.0)	0/32 (0.0)	2/109 (1.8)	0/62 (0.0)
RR [95%-CI]; p-value	NA		2.60 [0.12, 55.86], 0.5415		2.29 [0.11, 50.07], 0.5977	
OR [95%-CI]; p-value	NA		2.67 [0.12, 61.06], 0.5239		2.32 [0.10, 52.21], 0.5863	
RD [95%-CI]; p-value	NA		0.02 [-0.04, 0.09], 0.4835		0.01 [-0.02, 0.04], 0.5449	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	2/82 (2.4)	0/42 (0.0)	2/94 (2.1)	1/40 (2.5)	4/176 (2.3)	1/82 (1.2)
RR [95%-CI]; p-value	2.07 [0.10, 44.96], 0.6423		0.85 [0.08, 9.12], 0.8940		1.86 [0.21, 16.41], 0.5749	
OR [95%-CI]; p-value	2.10 [0.09, 47.62], 0.6339		0.85 [0.07, 9.63], 0.8939		1.88 [0.21, 17.12], 0.5677	
RD [95%-CI]; p-value	0.01 [-0.03, 0.06], 0.5949		-0.00 [-0.06, 0.05], 0.8972		0.01 [-0.02, 0.04], 0.5239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.8429		0.8119		0.8394	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	5/30 (16.7)	3/50 (6.0)	2/32 (6.3)	9/109 (8.3)	7/62 (11.3)
RR [95%-CI]; p-value	0.61 [0.20, 1.84], 0.3798		0.96 [0.17, 5.43], 0.9632		0.73 [0.29, 1.87], 0.5129	
OR [95%-CI]; p-value	0.57 [0.16, 2.03], 0.3787		0.96 [0.15, 6.07], 0.9632		0.71 [0.25, 2.00], 0.5126	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4085		-0.00 [-0.11, 0.10], 0.9633		-0.03 [-0.12, 0.06], 0.5280	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	4/82 (4.9)	4/42 (9.5)	7/94 (7.4)	4/40 (10.0)	11/176 (6.3)	8/82 (9.8)
RR [95%-CI]; p-value	0.51 [0.13, 1.95], 0.3260		0.74 [0.23, 2.40], 0.6218		0.64 [0.27, 1.53], 0.3170	
OR [95%-CI]; p-value	0.49 [0.12, 2.05], 0.3190		0.72 [0.20, 2.63], 0.6222		0.62 [0.24, 1.60], 0.3154	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3638		-0.03 [-0.13, 0.08], 0.6402		-0.04 [-0.11, 0.04], 0.3499	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8514		0.8949		0.9770	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	0/30 (0.0)	1/50 (2.0)	0/32 (0.0)	3/109 (2.8)	0/62 (0.0)
RR [95%-CI]; p-value	2.07 [0.10, 44.46], 0.6426		1.30 [0.04, 37.65], 0.8786		3.44 [0.18, 67.58], 0.4161	
OR [95%-CI]; p-value	2.11 [0.09, 48.17], 0.6338		1.31 [0.04, 40.08], 0.8782		3.51 [0.17, 71.22], 0.3842	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.5949		0.00 [-0.05, 0.06], 0.8748		0.02 [-0.02, 0.06], 0.3118	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	3/82 (3.7)	0/42 (0.0)	4/94 (4.3)	1/40 (2.5)	7/176 (4.0)	1/82 (1.2)
RR [95%-CI]; p-value	3.11 [0.16, 60.67], 0.4542		1.70 [0.20, 14.76], 0.6293		3.26 [0.41, 26.08], 0.2650	
OR [95%-CI]; p-value	3.19 [0.16, 65.18], 0.4269		1.73 [0.19, 16.01], 0.6237		3.36 [0.41, 27.73], 0.2341	
RD [95%-CI]; p-value	0.02 [-0.03, 0.08], 0.3493		0.02 [-0.05, 0.08], 0.5867		0.03 [-0.01, 0.06], 0.1483	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.6.s1
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.1876		0.3370		0.1404	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	9/59 (15.3)	10/30 (33.3)	11/50 (22.0)	6/32 (18.8)	20/109 (18.3)	16/62 (25.8)
RR [95%-CI]; p-value	0.46 [0.21, 1.00], 0.0513		1.17 [0.48, 2.86], 0.7249		0.71 [0.40, 1.27], 0.2481	
OR [95%-CI]; p-value	0.36 [0.13, 1.02], 0.0491		1.22 [0.40, 3.71], 0.7232		0.65 [0.31, 1.36], 0.2501	
RD [95%-CI]; p-value	-0.18 [-0.37, 0.01], 0.0650		0.03 [-0.14, 0.21], 0.7195		-0.07 [-0.21, 0.06], 0.2643	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	15/82 (18.3)	8/42 (19.0)	17/94 (18.1)	3/40 (7.5)	32/176 (18.2)	11/82 (13.4)
RR [95%-CI]; p-value	0.96 [0.44, 2.08], 0.9184		2.41 [0.75, 7.77], 0.1404		1.36 [0.72, 2.55], 0.3464	
OR [95%-CI]; p-value	0.95 [0.37, 2.47], 0.9185		2.72 [0.75, 9.88], 0.1156		1.43 [0.68, 3.01], 0.3387	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.14], 0.9189		0.11 [-0.01, 0.22], 0.0658		0.05 [-0.05, 0.14], 0.3161	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_6_m_pt_adr_age.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.8203		0.0333		0.0650	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	56/71 (78.9)	28/33 (84.8)	50/71 (70.4)	21/39 (53.8)	106/142 (74.6)	49/72 (68.1)
RR [95%-CI]; p-value	0.93 [0.77, 1.12], 0.4461		1.31 [0.94, 1.81], 0.1081		1.10 [0.91, 1.32], 0.3274	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4718		2.04 [0.91, 4.59], 0.0821		1.38 [0.74, 2.58], 0.3079	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4495		0.17 [-0.02, 0.35], 0.0857		0.07 [-0.06, 0.20], 0.3177	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	45/70 (64.3)	28/39 (71.8)	41/73 (56.2)	23/33 (69.7)	86/143 (60.1)	51/72 (70.8)
RR [95%-CI]; p-value	0.90 [0.69, 1.16], 0.4104		0.81 [0.60, 1.09], 0.1623		0.85 [0.70, 1.04], 0.1078	
OR [95%-CI]; p-value	0.71 [0.30, 1.66], 0.4243		0.56 [0.23, 1.34], 0.1872		0.62 [0.34, 1.14], 0.1238	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.11], 0.4146		-0.14 [-0.33, 0.06], 0.1710		-0.11 [-0.24, 0.03], 0.1127	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.3985		0.2945		0.9535	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	7/33 (21.2)	10/71 (14.1)	0/39 (0.0)	19/142 (13.4)	7/72 (9.7)
RR [95%-CI]; p-value	0.60 [0.24, 1.47], 0.2607		11.13 [0.67, 185.46], 0.0933		1.38 [0.61, 3.12], 0.4446	
OR [95%-CI]; p-value	0.54 [0.18, 1.60], 0.2615		12.79 [0.73, 225.19], 0.0277		1.43 [0.57, 3.59], 0.4390	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.07], 0.2942		0.13 [0.04, 0.22], 0.0044		0.04 [-0.05, 0.13], 0.4174	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	8/70 (11.4)	4/39 (10.3)	9/73 (12.3)	2/33 (6.1)	17/143 (11.9)	6/72 (8.3)
RR [95%-CI]; p-value	1.11 [0.36, 3.47], 0.8517		2.03 [0.46, 8.90], 0.3457		1.43 [0.59, 3.46], 0.4322	
OR [95%-CI]; p-value	1.13 [0.32, 4.02], 0.8513		2.18 [0.44, 10.70], 0.3272		1.48 [0.56, 3.94], 0.4261	
RD [95%-CI]; p-value	0.01 [-0.11, 0.13], 0.8493		0.06 [-0.05, 0.17], 0.2683		0.04 [-0.05, 0.12], 0.4012	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.9496		0.6109		0.7725	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	2/33 (6.1)	5/71 (7.0)	3/39 (7.7)	12/142 (8.5)	5/72 (6.9)
RR [95%-CI]; p-value	1.63 [0.36, 7.41], 0.5294		0.92 [0.23, 3.63], 0.9000		1.22 [0.45, 3.32], 0.7016	
OR [95%-CI]; p-value	1.70 [0.33, 8.64], 0.5214		0.91 [0.21, 4.03], 0.9001		1.24 [0.42, 3.66], 0.7002	
RD [95%-CI]; p-value	0.04 [-0.07, 0.14], 0.4863		-0.01 [-0.11, 0.10], 0.9012		0.02 [-0.06, 0.09], 0.6917	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	4/39 (10.3)	5/73 (6.8)	4/33 (12.1)	16/143 (11.2)	8/72 (11.1)
RR [95%-CI]; p-value	1.53 [0.52, 4.49], 0.4367		0.57 [0.16, 1.97], 0.3703		1.01 [0.45, 2.24], 0.9864	
OR [95%-CI]; p-value	1.63 [0.48, 5.52], 0.4278		0.53 [0.13, 2.13], 0.3673		1.01 [0.41, 2.48], 0.9864	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4026		-0.05 [-0.18, 0.07], 0.4104		0.00 [-0.09, 0.09], 0.9864	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.0763		0.7921		0.2207	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	15/71 (21.1)	2/33 (6.1)	8/71 (11.3)	5/39 (12.8)	23/142 (16.2)	7/72 (9.7)
RR [95%-CI]; p-value	3.49 [0.85, 14.37], 0.0840		0.88 [0.31, 2.50], 0.8090		1.67 [0.75, 3.70], 0.2095	
OR [95%-CI]; p-value	4.15 [0.89, 19.35], 0.0531		0.86 [0.26, 2.85], 0.8093		1.79 [0.73, 4.41], 0.1974	
RD [95%-CI]; p-value	0.15 [0.03, 0.28], 0.0182		-0.02 [-0.14, 0.11], 0.8122		0.06 [-0.03, 0.16], 0.1650	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	15/70 (21.4)	10/39 (25.6)	14/73 (19.2)	6/33 (18.2)	29/143 (20.3)	16/72 (22.2)
RR [95%-CI]; p-value	0.84 [0.42, 1.68], 0.6142		1.05 [0.44, 2.50], 0.9036		0.91 [0.53, 1.57], 0.7402	
OR [95%-CI]; p-value	0.79 [0.32, 1.98], 0.6161		1.07 [0.37, 3.08], 0.9034		0.89 [0.45, 1.77], 0.7411	
RD [95%-CI]; p-value	-0.04 [-0.21, 0.13], 0.6218		0.01 [-0.15, 0.17], 0.9026		-0.02 [-0.14, 0.10], 0.7437	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.0509		0.2467		0.4614	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	4/33 (12.1)	8/71 (11.3)	1/39 (2.6)	13/142 (9.2)	5/72 (6.9)
RR [95%-CI]; p-value	0.58 [0.17, 2.02], 0.3939		4.39 [0.57, 33.86], 0.1553		1.32 [0.49, 3.55], 0.5849	
OR [95%-CI]; p-value	0.55 [0.14, 2.19], 0.3912		4.83 [0.58, 40.10], 0.1111		1.35 [0.46, 3.95], 0.5820	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4305		0.09 [-0.00, 0.18], 0.0545		0.02 [-0.05, 0.10], 0.5660	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	1/39 (2.6)	7/73 (9.6)	3/33 (9.1)	18/143 (12.6)	4/72 (5.6)
RR [95%-CI]; p-value	6.13 [0.82, 45.71], 0.0770		1.05 [0.29, 3.83], 0.9353		2.27 [0.80, 6.45], 0.1253	
OR [95%-CI]; p-value	7.08 [0.88, 57.13], 0.0355		1.06 [0.26, 4.39], 0.9352		2.45 [0.80, 7.52], 0.1084	
RD [95%-CI]; p-value	0.13 [0.03, 0.23], 0.0090		0.00 [-0.11, 0.12], 0.9347		0.07 [-0.01, 0.15], 0.0693	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.4258		0.4057		0.9946	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	2/71 (2.8)	1/33 (3.0)	4/71 (5.6)	1/39 (2.6)	6/142 (4.2)	2/72 (2.8)
RR [95%-CI]; p-value	0.93 [0.09, 9.89], 0.9517		2.20 [0.25, 18.98], 0.4743		1.52 [0.31, 7.35], 0.6017	
OR [95%-CI]; p-value	0.93 [0.08, 10.61], 0.9517		2.27 [0.24, 21.04], 0.4597		1.54 [0.30, 7.85], 0.5979	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.07], 0.9524		0.03 [-0.04, 0.10], 0.4102		0.01 [-0.04, 0.06], 0.5731	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	6/70 (8.6)	1/39 (2.6)	3/73 (4.1)	2/33 (6.1)	9/143 (6.3)	3/72 (4.2)
RR [95%-CI]; p-value	3.34 [0.42, 26.77], 0.2556		0.68 [0.12, 3.87], 0.6619		1.51 [0.42, 5.41], 0.5263	
OR [95%-CI]; p-value	3.56 [0.41, 30.73], 0.2201		0.66 [0.11, 4.18], 0.6609		1.54 [0.41, 5.89], 0.5214	
RD [95%-CI]; p-value	0.06 [-0.02, 0.14], 0.1522		-0.02 [-0.11, 0.07], 0.6818		0.02 [-0.04, 0.08], 0.4940	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.4521		0.9213		0.6767	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	1/71 (1.4)	1/33 (3.0)	1/71 (1.4)	0/39 (0.0)	2/142 (1.4)	1/72 (1.4)
RR [95%-CI]; p-value	0.46 [0.03, 7.20], 0.5838		1.11 [0.04, 32.43], 0.9505		1.01 [0.09, 11.00], 0.9908	
OR [95%-CI]; p-value	0.46 [0.03, 7.54], 0.5751		1.11 [0.04, 33.97], 0.9505		1.01 [0.09, 11.38], 0.9908	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.05], 0.6226		0.00 [-0.04, 0.05], 0.9497		0.00 [-0.03, 0.03], 0.9908	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	2/70 (2.9)	0/39 (0.0)	2/73 (2.7)	1/33 (3.0)	4/143 (2.8)	1/72 (1.4)
RR [95%-CI]; p-value	2.26 [0.10, 48.83], 0.6038		0.90 [0.08, 9.62], 0.9334		2.01 [0.23, 17.69], 0.5277	
OR [95%-CI]; p-value	2.29 [0.10, 52.16], 0.5924		0.90 [0.08, 10.31], 0.9334		2.04 [0.22, 18.62], 0.5179	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5512		-0.00 [-0.07, 0.07], 0.9346		0.01 [-0.02, 0.05], 0.4702	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.1465		0.1536		0.0366	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	51/71 (71.8)	25/33 (75.8)	38/71 (53.5)	17/39 (43.6)	89/142 (62.7)	42/72 (58.3)
RR [95%-CI]; p-value	0.95 [0.74, 1.21], 0.6662		1.23 [0.81, 1.86], 0.3355		1.07 [0.85, 1.36], 0.5456	
OR [95%-CI]; p-value	0.82 [0.32, 2.11], 0.6744		1.49 [0.68, 3.27], 0.3190		1.20 [0.67, 2.14], 0.5379	
RD [95%-CI]; p-value	-0.04 [-0.22, 0.14], 0.6686		0.10 [-0.09, 0.29], 0.3160		0.04 [-0.10, 0.18], 0.5401	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	31/70 (44.3)	25/39 (64.1)	32/73 (43.8)	18/33 (54.5)	63/143 (44.1)	43/72 (59.7)
RR [95%-CI]; p-value	0.69 [0.49, 0.98], 0.0397		0.80 [0.54, 1.21], 0.2907		0.74 [0.57, 0.96], 0.0243	
OR [95%-CI]; p-value	0.45 [0.20, 1.00], 0.0472		0.65 [0.28, 1.49], 0.3064		0.53 [0.30, 0.94], 0.0301	
RD [95%-CI]; p-value	-0.20 [-0.39, -0.01], 0.0412		-0.11 [-0.31, 0.10], 0.3047		-0.16 [-0.30, -0.02], 0.0277	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.3233		0.0186		0.0118	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	24/71 (33.8)	10/33 (30.3)	28/71 (39.4)	6/39 (15.4)	52/142 (36.6)	16/72 (22.2)
RR [95%-CI]; p-value	1.12 [0.61, 2.06], 0.7260		2.56 [1.16, 5.65], 0.0196		1.65 [1.02, 2.67], 0.0428	
OR [95%-CI]; p-value	1.17 [0.48, 2.86], 0.7232		3.58 [1.33, 9.65], 0.0090		2.02 [1.05, 3.88], 0.0326	
RD [95%-CI]; p-value	0.03 [-0.16, 0.23], 0.7203		0.24 [0.08, 0.40], 0.0033		0.14 [0.02, 0.27], 0.0234	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	26/70 (37.1)	19/39 (48.7)	21/73 (28.8)	12/33 (36.4)	47/143 (32.9)	31/72 (43.1)
RR [95%-CI]; p-value	0.76 [0.49, 1.19], 0.2304		0.79 [0.44, 1.41], 0.4268		0.76 [0.54, 1.09], 0.1351	
OR [95%-CI]; p-value	0.62 [0.28, 1.38], 0.2394		0.71 [0.30, 1.69], 0.4342		0.65 [0.36, 1.16], 0.1425	
RD [95%-CI]; p-value	-0.12 [-0.31, 0.08], 0.2409		-0.08 [-0.27, 0.12], 0.4433		-0.10 [-0.24, 0.04], 0.1475	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.9496		0.6109		0.7725	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	2/33 (6.1)	5/71 (7.0)	3/39 (7.7)	12/142 (8.5)	5/72 (6.9)
RR [95%-CI]; p-value	1.63 [0.36, 7.41], 0.5294		0.92 [0.23, 3.63], 0.9000		1.22 [0.45, 3.32], 0.7016	
OR [95%-CI]; p-value	1.70 [0.33, 8.64], 0.5214		0.91 [0.21, 4.03], 0.9001		1.24 [0.42, 3.66], 0.7002	
RD [95%-CI]; p-value	0.04 [-0.07, 0.14], 0.4863		-0.01 [-0.11, 0.10], 0.9012		0.02 [-0.06, 0.09], 0.6917	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	4/39 (10.3)	5/73 (6.8)	4/33 (12.1)	16/143 (11.2)	8/72 (11.1)
RR [95%-CI]; p-value	1.53 [0.52, 4.49], 0.4367		0.57 [0.16, 1.97], 0.3703		1.01 [0.45, 2.24], 0.9864	
OR [95%-CI]; p-value	1.63 [0.48, 5.52], 0.4278		0.53 [0.13, 2.13], 0.3673		1.01 [0.41, 2.48], 0.9864	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4026		-0.05 [-0.18, 0.07], 0.4104		0.00 [-0.09, 0.09], 0.9864	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.5997		0.9912		0.5273	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	2/33 (6.1)	5/71 (7.0)	2/39 (5.1)	9/142 (6.3)	4/72 (5.6)
RR [95%-CI]; p-value	0.93 [0.18, 4.82], 0.9307		1.37 [0.28, 6.75], 0.6963		1.14 [0.36, 3.58], 0.8213	
OR [95%-CI]; p-value	0.93 [0.16, 5.32], 0.9308		1.40 [0.26, 7.58], 0.6940		1.15 [0.34, 3.87], 0.8209	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9316		0.02 [-0.07, 0.11], 0.6811		0.01 [-0.06, 0.07], 0.8173	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	6/73 (8.2)	2/33 (6.1)	13/143 (9.1)	9/72 (12.5)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		1.36 [0.29, 6.37], 0.6994		0.73 [0.33, 1.62], 0.4360	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		1.39 [0.26, 7.27], 0.6969		0.70 [0.28, 1.72], 0.4363	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		0.02 [-0.08, 0.12], 0.6811		-0.03 [-0.12, 0.06], 0.4566	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8351		0.3282		0.3739	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	16/71 (22.5)	10/33 (30.3)	15/71 (21.1)	3/39 (7.7)	31/142 (21.8)	13/72 (18.1)
RR [95%-CI]; p-value	0.74 [0.38, 1.46], 0.3888		2.75 [0.85, 8.91], 0.0923		1.21 [0.68, 2.16], 0.5227	
OR [95%-CI]; p-value	0.67 [0.26, 1.69], 0.3945		3.21 [0.87, 11.89], 0.0685		1.27 [0.62, 2.61], 0.5185	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.11], 0.4092		0.13 [0.01, 0.26], 0.0374		0.04 [-0.07, 0.15], 0.5082	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	12/70 (17.1)	10/39 (25.6)	11/73 (15.1)	4/33 (12.1)	23/143 (16.1)	14/72 (19.4)
RR [95%-CI]; p-value	0.67 [0.32, 1.40], 0.2877		1.24 [0.43, 3.62], 0.6896		0.83 [0.45, 1.51], 0.5361	
OR [95%-CI]; p-value	0.60 [0.23, 1.55], 0.2893		1.29 [0.38, 4.38], 0.6869		0.79 [0.38, 1.66], 0.5378	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.08], 0.3069		0.03 [-0.11, 0.17], 0.6762		-0.03 [-0.14, 0.08], 0.5474	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9269		0.2973		0.4477	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	7/33 (21.2)	7/71 (9.9)	3/39 (7.7)	17/142 (12.0)	10/72 (13.9)
RR [95%-CI]; p-value	0.66 [0.28, 1.59], 0.3580		1.28 [0.35, 4.68], 0.7072		0.86 [0.42, 1.78], 0.6892	
OR [95%-CI]; p-value	0.61 [0.21, 1.77], 0.3603		1.31 [0.32, 5.39], 0.7053		0.84 [0.36, 1.95], 0.6898	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.09], 0.3863		0.02 [-0.09, 0.13], 0.6959		-0.02 [-0.12, 0.08], 0.6958	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	8/39 (20.5)	10/73 (13.7)	8/33 (24.2)	19/143 (13.3)	16/72 (22.2)
RR [95%-CI]; p-value	0.63 [0.26, 1.49], 0.2916		0.57 [0.25, 1.30], 0.1797		0.60 [0.33, 1.09], 0.0939	
OR [95%-CI]; p-value	0.57 [0.20, 1.63], 0.2910		0.50 [0.18, 1.40], 0.1807		0.54 [0.26, 1.12], 0.0939	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3140		-0.11 [-0.27, 0.06], 0.2135		-0.09 [-0.20, 0.02], 0.1146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.3270		0.6637		0.2794	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	25/71 (35.2)	10/33 (30.3)	21/71 (29.6)	10/39 (25.6)	46/142 (32.4)	20/72 (27.8)
RR [95%-CI]; p-value	1.16 [0.63, 2.13], 0.6273		1.15 [0.61, 2.20], 0.6637		1.17 [0.75, 1.81], 0.4952	
OR [95%-CI]; p-value	1.25 [0.51, 3.04], 0.6220		1.22 [0.50, 2.94], 0.6607		1.25 [0.67, 2.33], 0.4896	
RD [95%-CI]; p-value	0.05 [-0.14, 0.24], 0.6167		0.04 [-0.13, 0.21], 0.6563		0.05 [-0.08, 0.18], 0.4829	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	13/70 (18.6)	10/39 (25.6)	12/73 (16.4)	6/33 (18.2)	25/143 (17.5)	16/72 (22.2)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3835		0.90 [0.37, 2.20], 0.8242		0.79 [0.45, 1.38], 0.4011	
OR [95%-CI]; p-value	0.66 [0.26, 1.69], 0.3859		0.89 [0.30, 2.61], 0.8248		0.74 [0.37, 1.50], 0.4038	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.09], 0.3998		-0.02 [-0.17, 0.14], 0.8273		-0.05 [-0.16, 0.07], 0.4169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8173		0.4316		0.5270	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	4/71 (5.6)	2/39 (5.1)	14/142 (9.9)	5/72 (6.9)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.21, 5.73], 0.9112		1.42 [0.53, 3.79], 0.4838	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.10 [0.19, 6.32], 0.9111		1.47 [0.51, 4.24], 0.4788	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.08, 0.09], 0.9099		0.03 [-0.05, 0.11], 0.4552	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	2/39 (5.1)	7/73 (9.6)	1/33 (3.0)	14/143 (9.8)	3/72 (4.2)
RR [95%-CI]; p-value	1.95 [0.43, 8.93], 0.3898		3.16 [0.41, 24.69], 0.2718		2.35 [0.70, 7.91], 0.1680	
OR [95%-CI]; p-value	2.06 [0.41, 10.42], 0.3757		3.39 [0.40, 28.77], 0.2365		2.50 [0.69, 8.98], 0.1493	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3331		0.07 [-0.02, 0.15], 0.1502		0.06 [-0.01, 0.12], 0.1005	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1992		0.8266		0.2485	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	6/71 (8.5)	3/39 (7.7)	16/142 (11.3)	6/72 (8.3)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.29, 4.15], 0.8898		1.35 [0.55, 3.31], 0.5086	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.11 [0.26, 4.70], 0.8896		1.40 [0.52, 3.74], 0.5043	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.10, 0.11], 0.8882		0.03 [-0.05, 0.11], 0.4849	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	8/73 (11.0)	4/33 (12.1)	15/143 (10.5)	11/72 (15.3)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		0.90 [0.29, 2.79], 0.8609		0.69 [0.33, 1.42], 0.3091	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		0.89 [0.25, 3.20], 0.8612		0.65 [0.28, 1.50], 0.3095	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		-0.01 [-0.14, 0.12], 0.8634		-0.05 [-0.14, 0.05], 0.3338	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0323		0.2866		0.3081	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	17/71 (23.9)	6/33 (18.2)	10/71 (14.1)	8/39 (20.5)	27/142 (19.0)	14/72 (19.4)
RR [95%-CI]; p-value	1.32 [0.57, 3.03], 0.5177		0.69 [0.30, 1.60], 0.3824		0.98 [0.55, 1.75], 0.9397	
OR [95%-CI]; p-value	1.42 [0.50, 4.00], 0.5099		0.64 [0.23, 1.77], 0.3833		0.97 [0.47, 2.00], 0.9397	
RD [95%-CI]; p-value	0.06 [-0.11, 0.22], 0.4933		-0.06 [-0.21, 0.09], 0.4021		-0.00 [-0.12, 0.11], 0.9399	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	15/39 (38.5)	15/73 (20.5)	5/33 (15.2)	26/143 (18.2)	20/72 (27.8)
RR [95%-CI]; p-value	0.41 [0.21, 0.80], 0.0091		1.36 [0.54, 3.42], 0.5185		0.65 [0.39, 1.09], 0.1030	
OR [95%-CI]; p-value	0.30 [0.12, 0.74], 0.0076		1.45 [0.48, 4.39], 0.5108		0.58 [0.30, 1.13], 0.1054	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.05], 0.0108		0.05 [-0.10, 0.21], 0.4907		-0.10 [-0.22, 0.03], 0.1208	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5879		0.1012		0.4410	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	13/71 (18.3)	13/33 (39.4)	14/71 (19.7)	6/39 (15.4)	27/142 (19.0)	19/72 (26.4)
RR [95%-CI]; p-value	0.46 [0.24, 0.89], 0.0206		1.28 [0.54, 3.07], 0.5774		0.72 [0.43, 1.20], 0.2112	
OR [95%-CI]; p-value	0.34 [0.14, 0.87], 0.0208		1.35 [0.47, 3.85], 0.5729		0.65 [0.33, 1.28], 0.2146	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.02], 0.0292		0.04 [-0.10, 0.19], 0.5614		-0.07 [-0.19, 0.05], 0.2305	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	10/39 (25.6)	8/73 (11.0)	8/33 (24.2)	19/143 (13.3)	18/72 (25.0)
RR [95%-CI]; p-value	0.61 [0.29, 1.31], 0.2076		0.45 [0.19, 1.10], 0.0802		0.53 [0.30, 0.95], 0.0324	
OR [95%-CI]; p-value	0.54 [0.21, 1.42], 0.2078		0.38 [0.13, 1.14], 0.0769		0.46 [0.22, 0.94], 0.0318	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2280		-0.13 [-0.30, 0.03], 0.1098		-0.12 [-0.23, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9989		0.6150		0.7564	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	7/33 (21.2)	11/71 (15.5)	4/39 (10.3)	18/142 (12.7)	11/72 (15.3)
RR [95%-CI]; p-value	0.46 [0.18, 1.22], 0.1188		1.51 [0.52, 4.43], 0.4523		0.83 [0.41, 1.66], 0.5983	
OR [95%-CI]; p-value	0.41 [0.13, 1.27], 0.1144		1.60 [0.47, 5.42], 0.4439		0.80 [0.36, 1.81], 0.5993	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.04], 0.1531		0.05 [-0.07, 0.18], 0.4193		-0.03 [-0.13, 0.07], 0.6083	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	9/73 (12.3)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		1.02 [0.34, 3.07], 0.9759		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		1.02 [0.29, 3.58], 0.9759		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		0.00 [-0.13, 0.14], 0.9759		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7918		0.1249		0.3349	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	6/33 (18.2)	12/71 (16.9)	3/39 (7.7)	21/142 (14.8)	9/72 (12.5)
RR [95%-CI]; p-value	0.70 [0.27, 1.80], 0.4553		2.20 [0.66, 7.32], 0.1998		1.18 [0.57, 2.45], 0.6506	
OR [95%-CI]; p-value	0.65 [0.21, 2.02], 0.4570		2.44 [0.64, 9.24], 0.1782		1.21 [0.53, 2.81], 0.6486	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4797		0.09 [-0.03, 0.21], 0.1351		0.02 [-0.07, 0.12], 0.6408	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	6/39 (15.4)	5/73 (6.8)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.84 [0.32, 2.17], 0.7129		0.57 [0.16, 1.97], 0.3703		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.81 [0.27, 2.48], 0.7135		0.53 [0.13, 2.13], 0.3673		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7191		-0.05 [-0.18, 0.07], 0.4104		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7563		0.0951		0.0960	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	3/33 (9.1)	7/71 (9.9)	0/39 (0.0)	11/142 (7.7)	3/72 (4.2)
RR [95%-CI]; p-value	0.62 [0.15, 2.61], 0.5145		7.79 [0.45, 133.66], 0.1570		1.86 [0.54, 6.45], 0.3288	
OR [95%-CI]; p-value	0.60 [0.13, 2.83], 0.5125		8.53 [0.47, 154.52], 0.0852		1.93 [0.52, 7.15], 0.3170	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.08], 0.5444		0.09 [0.01, 0.16], 0.0300		0.04 [-0.03, 0.10], 0.2711	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	8/73 (11.0)	6/33 (18.2)	13/143 (9.1)	12/72 (16.7)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		0.60 [0.23, 1.60], 0.3090		0.55 [0.26, 1.13], 0.1045	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		0.55 [0.18, 1.75], 0.3091		0.50 [0.22, 1.16], 0.1020	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		-0.07 [-0.22, 0.08], 0.3448		-0.08 [-0.17, 0.02], 0.1303	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7336		0.4179		0.7370	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	8/71 (11.3)	5/33 (15.2)	3/71 (4.2)	1/39 (2.6)	11/142 (7.7)	6/72 (8.3)
RR [95%-CI]; p-value	0.74 [0.26, 2.10], 0.5761		1.65 [0.18, 15.31], 0.6605		0.93 [0.36, 2.41], 0.8807	
OR [95%-CI]; p-value	0.71 [0.21, 2.37], 0.5772		1.68 [0.17, 16.68], 0.6561		0.92 [0.33, 2.61], 0.8808	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.10], 0.5938		0.02 [-0.05, 0.08], 0.6330		-0.01 [-0.08, 0.07], 0.8820	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	4/39 (10.3)	8/73 (11.0)	6/33 (18.2)	15/143 (10.5)	10/72 (13.9)
RR [95%-CI]; p-value	0.98 [0.30, 3.12], 0.9660		0.60 [0.23, 1.60], 0.3090		0.76 [0.36, 1.60], 0.4622	
OR [95%-CI]; p-value	0.97 [0.27, 3.55], 0.9660		0.55 [0.18, 1.75], 0.3091		0.73 [0.31, 1.71], 0.4630	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9661		-0.07 [-0.22, 0.08], 0.3448		-0.03 [-0.13, 0.06], 0.4801	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.3.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3715		0.9283		0.4007	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	3/71 (4.2)	8/33 (24.2)	3/71 (4.2)	0/39 (0.0)	6/142 (4.2)	8/72 (11.1)
RR [95%-CI]; p-value	0.17 [0.05, 0.62], 0.0066		3.34 [0.17, 64.97], 0.4261		0.38 [0.14, 1.05], 0.0631	
OR [95%-CI]; p-value	0.14 [0.03, 0.56], 0.0020		3.44 [0.17, 70.49], 0.3946		0.35 [0.12, 1.06], 0.0543	
RD [95%-CI]; p-value	-0.20 [-0.35, -0.05], 0.0106		0.03 [-0.03, 0.09], 0.3202		-0.07 [-0.15, 0.01], 0.0907	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	4/39 (10.3)	3/73 (4.1)	0/33 (0.0)	6/143 (4.2)	4/72 (5.6)
RR [95%-CI]; p-value	0.42 [0.10, 1.77], 0.2365		2.75 [0.14, 53.45], 0.5033		0.76 [0.22, 2.59], 0.6554	
OR [95%-CI]; p-value	0.39 [0.08, 1.85], 0.2229		2.83 [0.14, 58.10], 0.4818		0.74 [0.20, 2.73], 0.6550	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.2713		0.03 [-0.04, 0.09], 0.4029		-0.01 [-0.08, 0.05], 0.6687	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_3_m_pt_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.3.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0996		0.4314		0.3278	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	6/71 (8.5)	4/33 (12.1)	4/71 (5.6)	3/39 (7.7)	10/142 (7.0)	7/72 (9.7)
RR [95%-CI]; p-value	0.70 [0.21, 2.31], 0.5544		0.73 [0.17, 3.11], 0.6727		0.72 [0.29, 1.82], 0.4936	
OR [95%-CI]; p-value	0.67 [0.18, 2.55], 0.5545		0.72 [0.15, 3.38], 0.6722		0.70 [0.26, 1.93], 0.4933	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5764		-0.02 [-0.12, 0.08], 0.6847		-0.03 [-0.11, 0.05], 0.5132	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	1/70 (1.4)	6/39 (15.4)	3/73 (4.1)	0/33 (0.0)	4/143 (2.8)	6/72 (8.3)
RR [95%-CI]; p-value	0.09 [0.01, 0.74], 0.0252		2.75 [0.14, 53.45], 0.5033		0.34 [0.10, 1.15], 0.0827	
OR [95%-CI]; p-value	0.08 [0.01, 0.69], 0.0044		2.83 [0.14, 58.10], 0.4818		0.32 [0.09, 1.16], 0.0689	
RD [95%-CI]; p-value	-0.14 [-0.26, -0.02], 0.0190		0.03 [-0.04, 0.09], 0.4029		-0.06 [-0.12, 0.01], 0.1175	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_3_m_pt_ae10pct_sex.sas using SAS 9.4

Table 12.4.8.1.1.s2
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9994		0.2484		0.4182	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	3/71 (4.2)	1/33 (3.0)	1/71 (1.4)	2/39 (5.1)	4/142 (2.8)	3/72 (4.2)
RR [95%-CI]; p-value	1.39 [0.15, 12.91], 0.7697		0.27 [0.03, 2.93], 0.2849		0.68 [0.16, 2.94], 0.6017	
OR [95%-CI]; p-value	1.41 [0.14, 14.11], 0.7680		0.26 [0.02, 3.01], 0.2519		0.67 [0.15, 3.06], 0.5999	
RD [95%-CI]; p-value	0.01 [-0.06, 0.09], 0.7545		-0.04 [-0.11, 0.04], 0.3275		-0.01 [-0.07, 0.04], 0.6215	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	2/39 (5.1)	4/73 (5.5)	1/33 (3.0)	9/143 (6.3)	3/72 (4.2)
RR [95%-CI]; p-value	1.39 [0.28, 6.85], 0.6834		1.81 [0.21, 15.56], 0.5896		1.51 [0.42, 5.41], 0.5263	
OR [95%-CI]; p-value	1.42 [0.26, 7.70], 0.6809		1.86 [0.20, 17.27], 0.5818		1.54 [0.41, 5.89], 0.5214	
RD [95%-CI]; p-value	0.02 [-0.07, 0.11], 0.6672		0.02 [-0.05, 0.10], 0.5403		0.02 [-0.04, 0.08], 0.4940	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_8_1_1_m_soc_sae5pct_sex.sas using SAS 9.4

Table 12.4.8.1.2.s2
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_8_1_2_m_pt_sae5pct_sex.sas using SAS 9.4

Table 12.4.5.1.1.s2
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_5_1_1_m_soc_aeg35pct_sex.sas using SAS 9.4

Table 12.4.5.1.2.s2
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_5_1_2_m_pt_aeg35pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.5997		0.9912		0.5273	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	2/33 (6.1)	5/71 (7.0)	2/39 (5.1)	9/142 (6.3)	4/72 (5.6)
RR [95%-CI]; p-value	0.93 [0.18, 4.82], 0.9307		1.37 [0.28, 6.75], 0.6963		1.14 [0.36, 3.58], 0.8213	
OR [95%-CI]; p-value	0.93 [0.16, 5.32], 0.9308		1.40 [0.26, 7.58], 0.6940		1.15 [0.34, 3.87], 0.8209	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9316		0.02 [-0.07, 0.11], 0.6811		0.01 [-0.06, 0.07], 0.8173	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	6/73 (8.2)	2/33 (6.1)	13/143 (9.1)	9/72 (12.5)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		1.36 [0.29, 6.37], 0.6994		0.73 [0.33, 1.62], 0.4360	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		1.39 [0.26, 7.27], 0.6969		0.70 [0.28, 1.72], 0.4363	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		0.02 [-0.08, 0.12], 0.6811		-0.03 [-0.12, 0.06], 0.4566	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8351		0.3282		0.3739	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	16/71 (22.5)	10/33 (30.3)	15/71 (21.1)	3/39 (7.7)	31/142 (21.8)	13/72 (18.1)
RR [95%-CI]; p-value	0.74 [0.38, 1.46], 0.3888		2.75 [0.85, 8.91], 0.0923		1.21 [0.68, 2.16], 0.5227	
OR [95%-CI]; p-value	0.67 [0.26, 1.69], 0.3945		3.21 [0.87, 11.89], 0.0685		1.27 [0.62, 2.61], 0.5185	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.11], 0.4092		0.13 [0.01, 0.26], 0.0374		0.04 [-0.07, 0.15], 0.5082	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	12/70 (17.1)	10/39 (25.6)	11/73 (15.1)	4/33 (12.1)	23/143 (16.1)	14/72 (19.4)
RR [95%-CI]; p-value	0.67 [0.32, 1.40], 0.2877		1.24 [0.43, 3.62], 0.6896		0.83 [0.45, 1.51], 0.5361	
OR [95%-CI]; p-value	0.60 [0.23, 1.55], 0.2893		1.29 [0.38, 4.38], 0.6869		0.79 [0.38, 1.66], 0.5378	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.08], 0.3069		0.03 [-0.11, 0.17], 0.6762		-0.03 [-0.14, 0.08], 0.5474	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9269		0.2973		0.4477	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	7/33 (21.2)	7/71 (9.9)	3/39 (7.7)	17/142 (12.0)	10/72 (13.9)
RR [95%-CI]; p-value	0.66 [0.28, 1.59], 0.3580		1.28 [0.35, 4.68], 0.7072		0.86 [0.42, 1.78], 0.6892	
OR [95%-CI]; p-value	0.61 [0.21, 1.77], 0.3603		1.31 [0.32, 5.39], 0.7053		0.84 [0.36, 1.95], 0.6898	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.09], 0.3863		0.02 [-0.09, 0.13], 0.6959		-0.02 [-0.12, 0.08], 0.6958	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	8/39 (20.5)	10/73 (13.7)	8/33 (24.2)	19/143 (13.3)	16/72 (22.2)
RR [95%-CI]; p-value	0.63 [0.26, 1.49], 0.2916		0.57 [0.25, 1.30], 0.1797		0.60 [0.33, 1.09], 0.0939	
OR [95%-CI]; p-value	0.57 [0.20, 1.63], 0.2910		0.50 [0.18, 1.40], 0.1807		0.54 [0.26, 1.12], 0.0939	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3140		-0.11 [-0.27, 0.06], 0.2135		-0.09 [-0.20, 0.02], 0.1146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.3270		0.6637		0.2794	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	25/71 (35.2)	10/33 (30.3)	21/71 (29.6)	10/39 (25.6)	46/142 (32.4)	20/72 (27.8)
RR [95%-CI]; p-value	1.16 [0.63, 2.13], 0.6273		1.15 [0.61, 2.20], 0.6637		1.17 [0.75, 1.81], 0.4952	
OR [95%-CI]; p-value	1.25 [0.51, 3.04], 0.6220		1.22 [0.50, 2.94], 0.6607		1.25 [0.67, 2.33], 0.4896	
RD [95%-CI]; p-value	0.05 [-0.14, 0.24], 0.6167		0.04 [-0.13, 0.21], 0.6563		0.05 [-0.08, 0.18], 0.4829	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	13/70 (18.6)	10/39 (25.6)	12/73 (16.4)	6/33 (18.2)	25/143 (17.5)	16/72 (22.2)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3835		0.90 [0.37, 2.20], 0.8242		0.79 [0.45, 1.38], 0.4011	
OR [95%-CI]; p-value	0.66 [0.26, 1.69], 0.3859		0.89 [0.30, 2.61], 0.8248		0.74 [0.37, 1.50], 0.4038	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.09], 0.3998		-0.02 [-0.17, 0.14], 0.8273		-0.05 [-0.16, 0.07], 0.4169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8173		0.4316		0.5270	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	4/71 (5.6)	2/39 (5.1)	14/142 (9.9)	5/72 (6.9)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.21, 5.73], 0.9112		1.42 [0.53, 3.79], 0.4838	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.10 [0.19, 6.32], 0.9111		1.47 [0.51, 4.24], 0.4788	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.08, 0.09], 0.9099		0.03 [-0.05, 0.11], 0.4552	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	2/39 (5.1)	7/73 (9.6)	1/33 (3.0)	14/143 (9.8)	3/72 (4.2)
RR [95%-CI]; p-value	1.95 [0.43, 8.93], 0.3898		3.16 [0.41, 24.69], 0.2718		2.35 [0.70, 7.91], 0.1680	
OR [95%-CI]; p-value	2.06 [0.41, 10.42], 0.3757		3.39 [0.40, 28.77], 0.2365		2.50 [0.69, 8.98], 0.1493	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3331		0.07 [-0.02, 0.15], 0.1502		0.06 [-0.01, 0.12], 0.1005	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1992		0.8266		0.2485	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	6/71 (8.5)	3/39 (7.7)	16/142 (11.3)	6/72 (8.3)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.29, 4.15], 0.8898		1.35 [0.55, 3.31], 0.5086	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.11 [0.26, 4.70], 0.8896		1.40 [0.52, 3.74], 0.5043	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.10, 0.11], 0.8882		0.03 [-0.05, 0.11], 0.4849	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	8/73 (11.0)	4/33 (12.1)	15/143 (10.5)	11/72 (15.3)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		0.90 [0.29, 2.79], 0.8609		0.69 [0.33, 1.42], 0.3091	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		0.89 [0.25, 3.20], 0.8612		0.65 [0.28, 1.50], 0.3095	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		-0.01 [-0.14, 0.12], 0.8634		-0.05 [-0.14, 0.05], 0.3338	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0323		0.2866		0.3081	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	17/71 (23.9)	6/33 (18.2)	10/71 (14.1)	8/39 (20.5)	27/142 (19.0)	14/72 (19.4)
RR [95%-CI]; p-value	1.32 [0.57, 3.03], 0.5177		0.69 [0.30, 1.60], 0.3824		0.98 [0.55, 1.75], 0.9397	
OR [95%-CI]; p-value	1.42 [0.50, 4.00], 0.5099		0.64 [0.23, 1.77], 0.3833		0.97 [0.47, 2.00], 0.9397	
RD [95%-CI]; p-value	0.06 [-0.11, 0.22], 0.4933		-0.06 [-0.21, 0.09], 0.4021		-0.00 [-0.12, 0.11], 0.9399	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	15/39 (38.5)	15/73 (20.5)	5/33 (15.2)	26/143 (18.2)	20/72 (27.8)
RR [95%-CI]; p-value	0.41 [0.21, 0.80], 0.0091		1.36 [0.54, 3.42], 0.5185		0.65 [0.39, 1.09], 0.1030	
OR [95%-CI]; p-value	0.30 [0.12, 0.74], 0.0076		1.45 [0.48, 4.39], 0.5108		0.58 [0.30, 1.13], 0.1054	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.05], 0.0108		0.05 [-0.10, 0.21], 0.4907		-0.10 [-0.22, 0.03], 0.1208	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5879		0.1012		0.4410	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	13/71 (18.3)	13/33 (39.4)	14/71 (19.7)	6/39 (15.4)	27/142 (19.0)	19/72 (26.4)
RR [95%-CI]; p-value	0.46 [0.24, 0.89], 0.0206		1.28 [0.54, 3.07], 0.5774		0.72 [0.43, 1.20], 0.2112	
OR [95%-CI]; p-value	0.34 [0.14, 0.87], 0.0208		1.35 [0.47, 3.85], 0.5729		0.65 [0.33, 1.28], 0.2146	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.02], 0.0292		0.04 [-0.10, 0.19], 0.5614		-0.07 [-0.19, 0.05], 0.2305	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	10/39 (25.6)	8/73 (11.0)	8/33 (24.2)	19/143 (13.3)	18/72 (25.0)
RR [95%-CI]; p-value	0.61 [0.29, 1.31], 0.2076		0.45 [0.19, 1.10], 0.0802		0.53 [0.30, 0.95], 0.0324	
OR [95%-CI]; p-value	0.54 [0.21, 1.42], 0.2078		0.38 [0.13, 1.14], 0.0769		0.46 [0.22, 0.94], 0.0318	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2280		-0.13 [-0.30, 0.03], 0.1098		-0.12 [-0.23, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9989		0.6150		0.7564	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	7/33 (21.2)	11/71 (15.5)	4/39 (10.3)	18/142 (12.7)	11/72 (15.3)
RR [95%-CI]; p-value	0.46 [0.18, 1.22], 0.1188		1.51 [0.52, 4.43], 0.4523		0.83 [0.41, 1.66], 0.5983	
OR [95%-CI]; p-value	0.41 [0.13, 1.27], 0.1144		1.60 [0.47, 5.42], 0.4439		0.80 [0.36, 1.81], 0.5993	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.04], 0.1531		0.05 [-0.07, 0.18], 0.4193		-0.03 [-0.13, 0.07], 0.6083	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	9/73 (12.3)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		1.02 [0.34, 3.07], 0.9759		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		1.02 [0.29, 3.58], 0.9759		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		0.00 [-0.13, 0.14], 0.9759		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.4087		0.2542		0.1799	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	1/33 (3.0)	6/71 (8.5)	2/39 (5.1)	11/142 (7.7)	3/72 (4.2)
RR [95%-CI]; p-value	2.32 [0.28, 19.11], 0.4328		1.65 [0.35, 7.78], 0.5281		1.86 [0.54, 6.45], 0.3288	
OR [95%-CI]; p-value	2.42 [0.27, 21.62], 0.4141		1.71 [0.33, 8.90], 0.5209		1.93 [0.52, 7.15], 0.3170	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3460		0.03 [-0.06, 0.13], 0.4919		0.04 [-0.03, 0.10], 0.2711	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	6/70 (8.6)	4/39 (10.3)	6/73 (8.2)	5/33 (15.2)	12/143 (8.4)	9/72 (12.5)
RR [95%-CI]; p-value	0.84 [0.25, 2.78], 0.7700		0.54 [0.18, 1.65], 0.2816		0.67 [0.30, 1.52], 0.3388	
OR [95%-CI]; p-value	0.82 [0.22, 3.10], 0.7702		0.50 [0.14, 1.78], 0.2785		0.64 [0.26, 1.60], 0.3382	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.10], 0.7751		-0.07 [-0.21, 0.07], 0.3234		-0.04 [-0.13, 0.05], 0.3650	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7918		0.1249		0.3349	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	6/33 (18.2)	12/71 (16.9)	3/39 (7.7)	21/142 (14.8)	9/72 (12.5)
RR [95%-CI]; p-value	0.70 [0.27, 1.80], 0.4553		2.20 [0.66, 7.32], 0.1998		1.18 [0.57, 2.45], 0.6506	
OR [95%-CI]; p-value	0.65 [0.21, 2.02], 0.4570		2.44 [0.64, 9.24], 0.1782		1.21 [0.53, 2.81], 0.6486	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4797		0.09 [-0.03, 0.21], 0.1351		0.02 [-0.07, 0.12], 0.6408	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	6/39 (15.4)	5/73 (6.8)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.84 [0.32, 2.17], 0.7129		0.57 [0.16, 1.97], 0.3703		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.81 [0.27, 2.48], 0.7135		0.53 [0.13, 2.13], 0.3673		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7191		-0.05 [-0.18, 0.07], 0.4104		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7563		0.0951		0.0960	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	3/33 (9.1)	7/71 (9.9)	0/39 (0.0)	11/142 (7.7)	3/72 (4.2)
RR [95%-CI]; p-value	0.62 [0.15, 2.61], 0.5145		7.79 [0.45, 133.66], 0.1570		1.86 [0.54, 6.45], 0.3288	
OR [95%-CI]; p-value	0.60 [0.13, 2.83], 0.5125		8.53 [0.47, 154.52], 0.0852		1.93 [0.52, 7.15], 0.3170	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.08], 0.5444		0.09 [0.01, 0.16], 0.0300		0.04 [-0.03, 0.10], 0.2711	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	8/73 (11.0)	6/33 (18.2)	13/143 (9.1)	12/72 (16.7)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		0.60 [0.23, 1.60], 0.3090		0.55 [0.26, 1.13], 0.1045	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		0.55 [0.18, 1.75], 0.3091		0.50 [0.22, 1.16], 0.1020	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		-0.07 [-0.22, 0.08], 0.3448		-0.08 [-0.17, 0.02], 0.1303	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7336		0.4179		0.7370	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	8/71 (11.3)	5/33 (15.2)	3/71 (4.2)	1/39 (2.6)	11/142 (7.7)	6/72 (8.3)
RR [95%-CI]; p-value	0.74 [0.26, 2.10], 0.5761		1.65 [0.18, 15.31], 0.6605		0.93 [0.36, 2.41], 0.8807	
OR [95%-CI]; p-value	0.71 [0.21, 2.37], 0.5772		1.68 [0.17, 16.68], 0.6561		0.92 [0.33, 2.61], 0.8808	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.10], 0.5938		0.02 [-0.05, 0.08], 0.6330		-0.01 [-0.08, 0.07], 0.8820	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	4/39 (10.3)	8/73 (11.0)	6/33 (18.2)	15/143 (10.5)	10/72 (13.9)
RR [95%-CI]; p-value	0.98 [0.30, 3.12], 0.9660		0.60 [0.23, 1.60], 0.3090		0.76 [0.36, 1.60], 0.4622	
OR [95%-CI]; p-value	0.97 [0.27, 3.55], 0.9660		0.55 [0.18, 1.75], 0.3091		0.73 [0.31, 1.71], 0.4630	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9661		-0.07 [-0.22, 0.08], 0.3448		-0.03 [-0.13, 0.06], 0.4801	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.4.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3715		0.9283		0.4007	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	3/71 (4.2)	8/33 (24.2)	3/71 (4.2)	0/39 (0.0)	6/142 (4.2)	8/72 (11.1)
RR [95%-CI]; p-value	0.17 [0.05, 0.62], 0.0066		3.34 [0.17, 64.97], 0.4261		0.38 [0.14, 1.05], 0.0631	
OR [95%-CI]; p-value	0.14 [0.03, 0.56], 0.0020		3.44 [0.17, 70.49], 0.3946		0.35 [0.12, 1.06], 0.0543	
RD [95%-CI]; p-value	-0.20 [-0.35, -0.05], 0.0106		0.03 [-0.03, 0.09], 0.3202		-0.07 [-0.15, 0.01], 0.0907	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	4/39 (10.3)	3/73 (4.1)	0/33 (0.0)	6/143 (4.2)	4/72 (5.6)
RR [95%-CI]; p-value	0.42 [0.10, 1.77], 0.2365		2.75 [0.14, 53.45], 0.5033		0.76 [0.22, 2.59], 0.6554	
OR [95%-CI]; p-value	0.39 [0.08, 1.85], 0.2229		2.83 [0.14, 58.10], 0.4818		0.74 [0.20, 2.73], 0.6550	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.2713		0.03 [-0.04, 0.09], 0.4029		-0.01 [-0.08, 0.05], 0.6687	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_4_m_pt_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.4.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0996		0.4314		0.3278	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	6/71 (8.5)	4/33 (12.1)	4/71 (5.6)	3/39 (7.7)	10/142 (7.0)	7/72 (9.7)
RR [95%-CI]; p-value	0.70 [0.21, 2.31], 0.5544		0.73 [0.17, 3.11], 0.6727		0.72 [0.29, 1.82], 0.4936	
OR [95%-CI]; p-value	0.67 [0.18, 2.55], 0.5545		0.72 [0.15, 3.38], 0.6722		0.70 [0.26, 1.93], 0.4933	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5764		-0.02 [-0.12, 0.08], 0.6847		-0.03 [-0.11, 0.05], 0.5132	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	1/70 (1.4)	6/39 (15.4)	3/73 (4.1)	0/33 (0.0)	4/143 (2.8)	6/72 (8.3)
RR [95%-CI]; p-value	0.09 [0.01, 0.74], 0.0252		2.75 [0.14, 53.45], 0.5033		0.34 [0.10, 1.15], 0.0827	
OR [95%-CI]; p-value	0.08 [0.01, 0.69], 0.0044		2.83 [0.14, 58.10], 0.4818		0.32 [0.09, 1.16], 0.0689	
RD [95%-CI]; p-value	-0.14 [-0.26, -0.02], 0.0190		0.03 [-0.04, 0.09], 0.4029		-0.06 [-0.12, 0.01], 0.1175	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_4_m_pt_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.4.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.2103		0.5972		0.7253	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	4/33 (12.1)	2/71 (2.8)	1/39 (2.6)	7/142 (4.9)	5/72 (6.9)
RR [95%-CI]; p-value	0.58 [0.17, 2.02], 0.3939		1.10 [0.10, 11.73], 0.9380		0.71 [0.23, 2.16], 0.5459	
OR [95%-CI]; p-value	0.55 [0.14, 2.19], 0.3912		1.10 [0.10, 12.55], 0.9379		0.69 [0.21, 2.27], 0.5450	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4305		0.00 [-0.06, 0.07], 0.9371		-0.02 [-0.09, 0.05], 0.5652	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	1/39 (2.6)	6/73 (8.2)	5/33 (15.2)	11/143 (7.7)	6/72 (8.3)
RR [95%-CI]; p-value	2.79 [0.34, 23.00], 0.3415		0.54 [0.18, 1.65], 0.2816		0.92 [0.36, 2.40], 0.8693	
OR [95%-CI]; p-value	2.92 [0.33, 25.96], 0.3150		0.50 [0.14, 1.78], 0.2785		0.92 [0.32, 2.59], 0.8694	
RD [95%-CI]; p-value	0.05 [-0.03, 0.12], 0.2506		-0.07 [-0.21, 0.07], 0.3234		-0.01 [-0.08, 0.07], 0.8710	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_4_m_pt_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.8797		0.7901		0.6007	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	1/33 (3.0)	4/71 (5.6)	3/39 (7.7)	13/142 (9.2)	4/72 (5.6)
RR [95%-CI]; p-value	4.18 [0.55, 31.67], 0.1659		0.73 [0.17, 3.11], 0.6727		1.65 [0.56, 4.87], 0.3665	
OR [95%-CI]; p-value	4.65 [0.56, 38.30], 0.1204		0.72 [0.15, 3.38], 0.6722		1.71 [0.54, 5.46], 0.3576	
RD [95%-CI]; p-value	0.10 [-0.00, 0.19], 0.0513		-0.02 [-0.12, 0.08], 0.6847		0.04 [-0.04, 0.11], 0.3208	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	6/70 (8.6)	1/39 (2.6)	5/73 (6.8)	4/33 (12.1)	11/143 (7.7)	5/72 (6.9)
RR [95%-CI]; p-value	3.34 [0.42, 26.77], 0.2556		0.57 [0.16, 1.97], 0.3703		1.11 [0.40, 3.07], 0.8440	
OR [95%-CI]; p-value	3.56 [0.41, 30.73], 0.2201		0.53 [0.13, 2.13], 0.3673		1.12 [0.37, 3.35], 0.8437	
RD [95%-CI]; p-value	0.06 [-0.02, 0.14], 0.1522		-0.05 [-0.18, 0.07], 0.4104		0.01 [-0.07, 0.08], 0.8412	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5348		0.6179		0.2794	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	0/71 (0.0)	0/33 (0.0)	0/71 (0.0)	1/39 (2.6)	0/142 (0.0)	1/72 (1.4)
RR [95%-CI]; p-value	NA		0.27 [0.01, 7.95], 0.4502		0.25 [0.01, 7.44], 0.4254	
OR [95%-CI]; p-value	NA		0.27 [0.01, 8.16], 0.4182		0.25 [0.01, 7.54], 0.3890	
RD [95%-CI]; p-value	NA		-0.02 [-0.07, 0.03], 0.4924		-0.01 [-0.04, 0.02], 0.4787	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	2/70 (2.9)	0/39 (0.0)	1/73 (1.4)	0/33 (0.0)	3/143 (2.1)	0/72 (0.0)
RR [95%-CI]; p-value	2.26 [0.10, 48.83], 0.6038		0.92 [0.03, 26.69], 0.9602		3.04 [0.15, 59.92], 0.4644	
OR [95%-CI]; p-value	2.29 [0.10, 52.16], 0.5924		0.92 [0.03, 28.01], 0.9602		3.09 [0.15, 62.44], 0.4397	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5512		-0.00 [-0.05, 0.05], 0.9608		0.01 [-0.02, 0.04], 0.3614	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.6764		0.4109		0.2282	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	1/33 (3.0)	4/71 (5.6)	2/39 (5.1)	13/142 (9.2)	3/72 (4.2)
RR [95%-CI]; p-value	4.18 [0.55, 31.67], 0.1659		1.10 [0.21, 5.73], 0.9112		2.20 [0.65, 7.46], 0.2071	
OR [95%-CI]; p-value	4.65 [0.56, 38.30], 0.1204		1.10 [0.19, 6.32], 0.9111		2.32 [0.64, 8.41], 0.1899	
RD [95%-CI]; p-value	0.10 [-0.00, 0.19], 0.0513		0.01 [-0.08, 0.09], 0.9099		0.05 [-0.02, 0.12], 0.1396	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	4/70 (5.7)	1/39 (2.6)	4/73 (5.5)	4/33 (12.1)	8/143 (5.6)	5/72 (6.9)
RR [95%-CI]; p-value	2.23 [0.26, 19.25], 0.4663		0.45 [0.12, 1.70], 0.2397		0.81 [0.27, 2.37], 0.6951	
OR [95%-CI]; p-value	2.30 [0.25, 21.36], 0.4511		0.42 [0.10, 1.80], 0.2307		0.79 [0.25, 2.52], 0.6951	
RD [95%-CI]; p-value	0.03 [-0.04, 0.11], 0.4016		-0.07 [-0.19, 0.06], 0.2898		-0.01 [-0.08, 0.06], 0.7045	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.7486		0.8297		0.7053	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	1/33 (3.0)	1/71 (1.4)	0/39 (0.0)	5/142 (3.5)	1/72 (1.4)
RR [95%-CI]; p-value	1.86 [0.22, 15.99], 0.5722		1.11 [0.04, 32.43], 0.9505		2.54 [0.30, 21.30], 0.3916	
OR [95%-CI]; p-value	1.91 [0.21, 17.79], 0.5635		1.11 [0.04, 33.97], 0.9505		2.59 [0.30, 22.61], 0.3720	
RD [95%-CI]; p-value	0.03 [-0.05, 0.11], 0.5202		0.00 [-0.04, 0.05], 0.9497		0.02 [-0.02, 0.06], 0.3035	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	0/39 (0.0)	2/73 (2.7)	0/33 (0.0)	5/143 (3.5)	0/72 (0.0)
RR [95%-CI]; p-value	3.39 [0.17, 65.89], 0.4207		1.84 [0.09, 39.62], 0.6984		5.07 [0.28, 91.53], 0.2715	
OR [95%-CI]; p-value	3.49 [0.17, 71.55], 0.3883		1.86 [0.08, 42.37], 0.6930		5.22 [0.28, 96.84], 0.2170	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3148		0.01 [-0.04, 0.07], 0.6600		0.03 [-0.01, 0.06], 0.1226	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8404		0.9394		0.8494	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	3/33 (9.1)	4/71 (5.6)	2/39 (5.1)	9/142 (6.3)	5/72 (6.9)
RR [95%-CI]; p-value	0.77 [0.20, 3.05], 0.7150		1.10 [0.21, 5.73], 0.9112		0.91 [0.32, 2.62], 0.8653	
OR [95%-CI]; p-value	0.76 [0.17, 3.38], 0.7152		1.10 [0.19, 6.32], 0.9111		0.91 [0.29, 2.81], 0.8654	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.09], 0.7263		0.01 [-0.08, 0.09], 0.9099		-0.01 [-0.08, 0.07], 0.8672	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	6/39 (15.4)	9/73 (12.3)	4/33 (12.1)	16/143 (11.2)	10/72 (13.9)
RR [95%-CI]; p-value	0.65 [0.23, 1.80], 0.4067		1.02 [0.34, 3.07], 0.9759		0.81 [0.39, 1.68], 0.5657	
OR [95%-CI]; p-value	0.61 [0.19, 1.97], 0.4057		1.02 [0.29, 3.58], 0.9759		0.78 [0.34, 1.82], 0.5666	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.08], 0.4284		0.00 [-0.13, 0.14], 0.9759		-0.03 [-0.12, 0.07], 0.5780	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5348		0.9235		0.6581	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	0/71 (0.0)	0/33 (0.0)	1/71 (1.4)	0/39 (0.0)	1/142 (0.7)	0/72 (0.0)
RR [95%-CI]; p-value	NA		1.11 [0.04, 32.43], 0.9505		1.02 [0.03, 30.08], 0.9903	
OR [95%-CI]; p-value	NA		1.11 [0.04, 33.97], 0.9505		1.02 [0.03, 30.80], 0.9903	
RD [95%-CI]; p-value	NA		0.00 [-0.04, 0.05], 0.9497		0.00 [-0.02, 0.02], 0.9903	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	2/70 (2.9)	0/39 (0.0)	3/73 (4.1)	1/33 (3.0)	5/143 (3.5)	1/72 (1.4)
RR [95%-CI]; p-value	2.26 [0.10, 48.83], 0.6038		1.36 [0.15, 12.56], 0.7885		2.52 [0.30, 21.15], 0.3952	
OR [95%-CI]; p-value	2.29 [0.10, 52.16], 0.5924		1.37 [0.14, 13.70], 0.7872		2.57 [0.29, 22.44], 0.3759	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5512		0.01 [-0.06, 0.08], 0.7754		0.02 [-0.02, 0.06], 0.3073	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.5708		0.9696		0.6661	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	3/33 (9.1)	3/71 (4.2)	2/39 (5.1)	8/142 (5.6)	5/72 (6.9)
RR [95%-CI]; p-value	0.77 [0.20, 3.05], 0.7150		0.82 [0.14, 4.72], 0.8279		0.81 [0.28, 2.39], 0.7045	
OR [95%-CI]; p-value	0.76 [0.17, 3.38], 0.7152		0.82 [0.13, 5.11], 0.8278		0.80 [0.25, 2.54], 0.7045	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.09], 0.7263		-0.01 [-0.09, 0.07], 0.8323		-0.01 [-0.08, 0.06], 0.7132	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	7/73 (9.6)	4/33 (12.1)	12/143 (8.4)	10/72 (13.9)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		0.79 [0.25, 2.52], 0.6916		0.60 [0.27, 1.33], 0.2113	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		0.77 [0.21, 2.83], 0.6922		0.57 [0.23, 1.39], 0.2094	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		-0.03 [-0.16, 0.10], 0.7032		-0.05 [-0.15, 0.04], 0.2410	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.7886		0.8120		0.9397	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	2/71 (2.8)	0/33 (0.0)	1/71 (1.4)	0/39 (0.0)	3/142 (2.1)	0/72 (0.0)
RR [95%-CI]; p-value	1.89 [0.09, 40.72], 0.6853		1.11 [0.04, 32.43], 0.9505		3.06 [0.16, 60.34], 0.4616	
OR [95%-CI]; p-value	1.91 [0.08, 43.61], 0.6793		1.11 [0.04, 33.97], 0.9505		3.11 [0.15, 62.89], 0.4365	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.6446		0.00 [-0.04, 0.05], 0.9497		0.01 [-0.02, 0.04], 0.3584	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	0/39 (0.0)	4/73 (5.5)	1/33 (3.0)	7/143 (4.9)	1/72 (1.4)
RR [95%-CI]; p-value	3.39 [0.17, 65.89], 0.4207		1.81 [0.21, 15.56], 0.5896		3.52 [0.44, 28.10], 0.2343	
OR [95%-CI]; p-value	3.49 [0.17, 71.55], 0.3883		1.86 [0.20, 17.27], 0.5818		3.65 [0.44, 30.29], 0.1999	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3148		0.02 [-0.05, 0.10], 0.5403		0.04 [-0.01, 0.08], 0.1226	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.6.s2
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.4079		0.8723		0.6233	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	13/71 (18.3)	11/33 (33.3)	15/71 (21.1)	5/39 (12.8)	28/142 (19.7)	16/72 (22.2)
RR [95%-CI]; p-value	0.55 [0.28, 1.09], 0.0882		1.65 [0.65, 4.19], 0.2944		0.89 [0.51, 1.53], 0.6672	
OR [95%-CI]; p-value	0.45 [0.17, 1.15], 0.0906		1.82 [0.61, 5.46], 0.2799		0.86 [0.43, 1.72], 0.6685	
RD [95%-CI]; p-value	-0.15 [-0.33, 0.03], 0.1101		0.08 [-0.06, 0.22], 0.2500		-0.03 [-0.14, 0.09], 0.6728	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	7/39 (17.9)	13/73 (17.8)	4/33 (12.1)	24/143 (16.8)	11/72 (15.3)
RR [95%-CI]; p-value	0.88 [0.37, 2.08], 0.7627		1.47 [0.52, 4.17], 0.4695		1.10 [0.57, 2.11], 0.7786	
OR [95%-CI]; p-value	0.85 [0.30, 2.41], 0.7633		1.57 [0.47, 5.24], 0.4600		1.12 [0.51, 2.43], 0.7778	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.13], 0.7666		0.06 [-0.08, 0.20], 0.4318		0.02 [-0.09, 0.12], 0.7750	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_6_m_pt_adr_sex.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.4273		0.2512		0.2367	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	52/73 (71.2)	26/36 (72.2)	49/77 (63.6)	15/29 (51.7)	101/150 (67.3)	41/65 (63.1)
RR [95%-CI]; p-value	0.99 [0.77, 1.27], 0.9137		1.23 [0.83, 1.82], 0.2977		1.07 [0.86, 1.33], 0.5550	
OR [95%-CI]; p-value	0.95 [0.39, 2.31], 0.9142		1.63 [0.69, 3.87], 0.2636		1.21 [0.66, 2.22], 0.5450	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9139		0.12 [-0.09, 0.33], 0.2690		0.04 [-0.10, 0.18], 0.5492	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	49/68 (72.1)	30/36 (83.3)	42/67 (62.7)	29/43 (67.4)	91/135 (67.4)	59/79 (74.7)
RR [95%-CI]; p-value	0.86 [0.70, 1.06], 0.1707		0.93 [0.70, 1.23], 0.6061		0.90 [0.76, 1.07], 0.2480	
OR [95%-CI]; p-value	0.52 [0.19, 1.44], 0.2005		0.81 [0.36, 1.82], 0.6109		0.70 [0.38, 1.31], 0.2619	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.05], 0.1721		-0.05 [-0.23, 0.13], 0.6081		-0.07 [-0.20, 0.05], 0.2512	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.7123		0.3201		0.2391	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	11/77 (14.3)	2/29 (6.9)	21/150 (14.0)	9/65 (13.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		2.07 [0.49, 8.79], 0.3232		1.01 [0.49, 2.09], 0.9762	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		2.25 [0.47, 10.83], 0.3012		1.01 [0.44, 2.35], 0.9761	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		0.07 [-0.05, 0.19], 0.2309		0.00 [-0.10, 0.10], 0.9761	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	4/36 (11.1)	8/67 (11.9)	0/43 (0.0)	15/135 (11.1)	4/79 (5.1)
RR [95%-CI]; p-value	0.93 [0.29, 2.96], 0.8973		10.39 [0.61, 176.30], 0.1052		2.19 [0.75, 6.38], 0.1490	
OR [95%-CI]; p-value	0.92 [0.25, 3.37], 0.8974		11.66 [0.65, 208.57], 0.0375		2.34 [0.75, 7.33], 0.1333	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.8985		0.11 [0.02, 0.19], 0.0117		0.06 [-0.01, 0.13], 0.0985	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.2083		0.3010		0.9961	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	5/36 (13.9)	5/77 (6.5)	1/29 (3.4)	15/150 (10.0)	6/65 (9.2)
RR [95%-CI]; p-value	0.99 [0.36, 2.67], 0.9784		1.88 [0.23, 15.44], 0.5555		1.08 [0.44, 2.67], 0.8618	
OR [95%-CI]; p-value	0.98 [0.31, 3.13], 0.9784		1.94 [0.22, 17.39], 0.5453		1.09 [0.40, 2.95], 0.8615	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.14], 0.9784		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.08, 0.09], 0.8595	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	1/36 (2.8)	5/67 (7.5)	6/43 (14.0)	13/135 (9.6)	7/79 (8.9)
RR [95%-CI]; p-value	4.24 [0.55, 32.55], 0.1653		0.53 [0.17, 1.64], 0.2749		1.09 [0.45, 2.61], 0.8523	
OR [95%-CI]; p-value	4.67 [0.56, 38.89], 0.1210		0.50 [0.14, 1.74], 0.2682		1.10 [0.42, 2.87], 0.8521	
RD [95%-CI]; p-value	0.09 [-0.00, 0.18], 0.0596		-0.06 [-0.19, 0.06], 0.2938		0.01 [-0.07, 0.09], 0.8506	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.4535		0.2761		0.2185	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	14/73 (19.2)	4/36 (11.1)	13/77 (16.9)	3/29 (10.3)	27/150 (18.0)	7/65 (10.8)
RR [95%-CI]; p-value	1.73 [0.61, 4.87], 0.3023		1.63 [0.50, 5.31], 0.4161		1.67 [0.77, 3.64], 0.1960	
OR [95%-CI]; p-value	1.90 [0.58, 6.25], 0.2861		1.76 [0.46, 6.69], 0.4019		1.82 [0.75, 4.42], 0.1820	
RD [95%-CI]; p-value	0.08 [-0.06, 0.22], 0.2475		0.07 [-0.07, 0.20], 0.3561		0.07 [-0.02, 0.17], 0.1451	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	16/68 (23.5)	8/36 (22.2)	9/67 (13.4)	8/43 (18.6)	25/135 (18.5)	16/79 (20.3)
RR [95%-CI]; p-value	1.06 [0.50, 2.23], 0.8807		0.72 [0.30, 1.73], 0.4641		0.91 [0.52, 1.61], 0.7551	
OR [95%-CI]; p-value	1.08 [0.41, 2.83], 0.8803		0.68 [0.24, 1.92], 0.4640		0.89 [0.44, 1.80], 0.7557	
RD [95%-CI]; p-value	0.01 [-0.16, 0.18], 0.8796		-0.05 [-0.19, 0.09], 0.4757		-0.02 [-0.13, 0.09], 0.7577	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.4675		0.3116		0.8734	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	7/73 (9.6)	3/36 (8.3)	10/77 (13.0)	1/29 (3.4)	17/150 (11.3)	4/65 (6.2)
RR [95%-CI]; p-value	1.15 [0.32, 4.19], 0.8314		3.77 [0.50, 28.13], 0.1962		1.84 [0.64, 5.26], 0.2541	
OR [95%-CI]; p-value	1.17 [0.28, 4.81], 0.8309		4.18 [0.51, 34.21], 0.1511		1.95 [0.63, 6.04], 0.2400	
RD [95%-CI]; p-value	0.01 [-0.10, 0.13], 0.8272		0.10 [-0.00, 0.20], 0.0622		0.05 [-0.03, 0.13], 0.1895	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	2/36 (5.6)	5/67 (7.5)	3/43 (7.0)	14/135 (10.4)	5/79 (6.3)
RR [95%-CI]; p-value	2.38 [0.54, 10.44], 0.2497		1.07 [0.27, 4.25], 0.9238		1.64 [0.61, 4.38], 0.3247	
OR [95%-CI]; p-value	2.59 [0.53, 12.71], 0.2257		1.08 [0.24, 4.75], 0.9237		1.71 [0.59, 4.95], 0.3159	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1710		0.00 [-0.09, 0.10], 0.9232		0.04 [-0.03, 0.11], 0.2867	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.3890		0.3528		0.8167	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	2/36 (5.6)	4/77 (5.2)	0/29 (0.0)	8/150 (5.3)	2/65 (3.1)
RR [95%-CI]; p-value	0.99 [0.19, 5.13], 0.9869		3.06 [0.17, 56.21], 0.4505		1.73 [0.38, 7.94], 0.4787	
OR [95%-CI]; p-value	0.99 [0.17, 5.65], 0.9869		3.18 [0.16, 62.02], 0.4217		1.77 [0.37, 8.60], 0.4706	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.09], 0.9870		0.03 [-0.03, 0.10], 0.3132		0.02 [-0.03, 0.08], 0.4237	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	0/36 (0.0)	3/67 (4.5)	3/43 (7.0)	7/135 (5.2)	3/79 (3.8)
RR [95%-CI]; p-value	4.29 [0.23, 79.01], 0.3267		0.64 [0.14, 3.04], 0.5759		1.37 [0.36, 5.13], 0.6447	
OR [95%-CI]; p-value	4.50 [0.23, 87.55], 0.2787		0.63 [0.12, 3.25], 0.5733		1.39 [0.35, 5.52], 0.6425	
RD [95%-CI]; p-value	0.05 [-0.02, 0.11], 0.1898		-0.02 [-0.12, 0.07], 0.5897		0.01 [-0.04, 0.07], 0.6293	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.4839		0.8060		0.5460	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	1/73 (1.4)	1/36 (2.8)	1/77 (1.3)	0/29 (0.0)	2/150 (1.3)	1/65 (1.5)
RR [95%-CI]; p-value	0.49 [0.03, 7.66], 0.6135		0.77 [0.03, 22.24], 0.8769		0.87 [0.08, 9.39], 0.9063	
OR [95%-CI]; p-value	0.49 [0.03, 8.00], 0.6065		0.76 [0.02, 23.37], 0.8766		0.86 [0.08, 9.71], 0.9063	
RD [95%-CI]; p-value	-0.01 [-0.07, 0.05], 0.6452		-0.00 [-0.06, 0.05], 0.8835		-0.00 [-0.04, 0.03], 0.9088	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	0/36 (0.0)	2/67 (3.0)	1/43 (2.3)	4/135 (3.0)	1/79 (1.3)
RR [95%-CI]; p-value	2.15 [0.10, 46.38], 0.6260		1.28 [0.12, 13.73], 0.8364		2.34 [0.27, 20.58], 0.4432	
OR [95%-CI]; p-value	2.18 [0.10, 49.68], 0.6163		1.29 [0.11, 14.70], 0.8358		2.38 [0.26, 21.69], 0.4277	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5761		0.01 [-0.05, 0.07], 0.8315		0.02 [-0.02, 0.05], 0.3784	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.5576		0.1409		0.2253	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	45/73 (61.6)	25/36 (69.4)	39/77 (50.6)	11/29 (37.9)	84/150 (56.0)	36/65 (55.4)
RR [95%-CI]; p-value	0.89 [0.67, 1.18], 0.4081		1.34 [0.80, 2.24], 0.2713		1.01 [0.78, 1.31], 0.9337	
OR [95%-CI]; p-value	0.71 [0.30, 1.66], 0.4243		1.68 [0.70, 4.02], 0.2423		1.03 [0.57, 1.84], 0.9335	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.11], 0.4144		0.13 [-0.08, 0.34], 0.2329		0.01 [-0.14, 0.15], 0.9335	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	37/68 (54.4)	25/36 (69.4)	31/67 (46.3)	24/43 (55.8)	68/135 (50.4)	49/79 (62.0)
RR [95%-CI]; p-value	0.78 [0.58, 1.07], 0.1194		0.83 [0.57, 1.20], 0.3212		0.81 [0.64, 1.03], 0.0898	
OR [95%-CI]; p-value	0.53 [0.22, 1.23], 0.1372		0.68 [0.32, 1.47], 0.3286		0.62 [0.35, 1.09], 0.0984	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.04], 0.1238		-0.10 [-0.29, 0.10], 0.3260		-0.12 [-0.25, 0.02], 0.0937	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.9489		0.9309		0.9440	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	23/73 (31.5)	13/36 (36.1)	26/77 (33.8)	7/29 (24.1)	49/150 (32.7)	20/65 (30.8)
RR [95%-CI]; p-value	0.87 [0.50, 1.51], 0.6273		1.40 [0.68, 2.87], 0.3589		1.06 [0.69, 1.63], 0.7855	
OR [95%-CI]; p-value	0.81 [0.35, 1.89], 0.6307		1.60 [0.61, 4.24], 0.3399		1.09 [0.58, 2.04], 0.7843	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6342		0.10 [-0.09, 0.28], 0.3160		0.02 [-0.12, 0.15], 0.7829	
2.Baseline Weight ≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	27/68 (39.7)	16/36 (44.4)	23/67 (34.3)	11/43 (25.6)	50/135 (37.0)	27/79 (34.2)
RR [95%-CI]; p-value	0.89 [0.56, 1.43], 0.6369		1.34 [0.73, 2.46], 0.3430		1.08 [0.74, 1.58], 0.6760	
OR [95%-CI]; p-value	0.82 [0.36, 1.86], 0.6406		1.52 [0.65, 3.56], 0.3327		1.13 [0.63, 2.03], 0.6740	
RD [95%-CI]; p-value	-0.05 [-0.25, 0.15], 0.6418		0.09 [-0.09, 0.26], 0.3217		0.03 [-0.10, 0.16], 0.6724	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.2083		0.3010		0.9961	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	5/36 (13.9)	5/77 (6.5)	1/29 (3.4)	15/150 (10.0)	6/65 (9.2)
RR [95%-CI]; p-value	0.99 [0.36, 2.67], 0.9784		1.88 [0.23, 15.44], 0.5555		1.08 [0.44, 2.67], 0.8618	
OR [95%-CI]; p-value	0.98 [0.31, 3.13], 0.9784		1.94 [0.22, 17.39], 0.5453		1.09 [0.40, 2.95], 0.8615	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.14], 0.9784		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.08, 0.09], 0.8595	
2.Baseline Weight ≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	1/36 (2.8)	5/67 (7.5)	6/43 (14.0)	13/135 (9.6)	7/79 (8.9)
RR [95%-CI]; p-value	4.24 [0.55, 32.55], 0.1653		0.53 [0.17, 1.64], 0.2749		1.09 [0.45, 2.61], 0.8523	
OR [95%-CI]; p-value	4.67 [0.56, 38.89], 0.1210		0.50 [0.14, 1.74], 0.2682		1.10 [0.42, 2.87], 0.8521	
RD [95%-CI]; p-value	0.09 [-0.00, 0.18], 0.0596		-0.06 [-0.19, 0.06], 0.2938		0.01 [-0.07, 0.09], 0.8506	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6190		0.7629		0.6433	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	3/36 (8.3)	5/77 (6.5)	1/29 (3.4)	10/150 (6.7)	4/65 (6.2)
RR [95%-CI]; p-value	0.82 [0.21, 3.25], 0.7798		1.88 [0.23, 15.44], 0.5555		1.08 [0.35, 3.33], 0.8888	
OR [95%-CI]; p-value	0.81 [0.18, 3.59], 0.7799		1.94 [0.22, 17.39], 0.5453		1.09 [0.33, 3.61], 0.8887	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.09], 0.7863		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.07, 0.08], 0.8870	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	6/67 (9.0)	3/43 (7.0)	12/135 (8.9)	9/79 (11.4)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		1.28 [0.34, 4.86], 0.7133		0.78 [0.34, 1.77], 0.5524	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		1.31 [0.31, 5.55], 0.7118		0.76 [0.30, 1.89], 0.5525	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		0.02 [-0.08, 0.12], 0.7047		-0.03 [-0.11, 0.06], 0.5634	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1702		0.9337		0.6054	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	18/73 (24.7)	9/36 (25.0)	11/77 (14.3)	2/29 (6.9)	29/150 (19.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.99 [0.49, 1.97], 0.9689		2.07 [0.49, 8.79], 0.3232		1.14 [0.61, 2.15], 0.6787	
OR [95%-CI]; p-value	0.98 [0.39, 2.47], 0.9689		2.25 [0.47, 10.83], 0.3012		1.18 [0.55, 2.53], 0.6766	
RD [95%-CI]; p-value	-0.00 [-0.18, 0.17], 0.9690		0.07 [-0.05, 0.19], 0.2309		0.02 [-0.09, 0.14], 0.6702	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	10/68 (14.7)	11/36 (30.6)	15/67 (22.4)	5/43 (11.6)	25/135 (18.5)	16/79 (20.3)
RR [95%-CI]; p-value	0.48 [0.23, 1.02], 0.0577		1.93 [0.75, 4.91], 0.1705		0.91 [0.52, 1.61], 0.7551	
OR [95%-CI]; p-value	0.39 [0.15, 1.04], 0.0554		2.19 [0.73, 6.55], 0.1534		0.89 [0.44, 1.80], 0.7557	
RD [95%-CI]; p-value	-0.16 [-0.33, 0.01], 0.0716		0.11 [-0.03, 0.25], 0.1274		-0.02 [-0.13, 0.09], 0.7577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7893		0.6563		0.8313	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	7/77 (9.1)	4/29 (13.8)	17/150 (11.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		0.66 [0.21, 2.09], 0.4781		0.67 [0.33, 1.35], 0.2618	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		0.63 [0.17, 2.32], 0.4791		0.63 [0.28, 1.43], 0.2634	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		-0.05 [-0.19, 0.09], 0.5133		-0.06 [-0.16, 0.05], 0.2936	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	8/36 (22.2)	10/67 (14.9)	7/43 (16.3)	19/135 (14.1)	15/79 (19.0)
RR [95%-CI]; p-value	0.60 [0.25, 1.41], 0.2389		0.92 [0.38, 2.23], 0.8478		0.74 [0.40, 1.37], 0.3418	
OR [95%-CI]; p-value	0.53 [0.19, 1.53], 0.2384		0.90 [0.32, 2.58], 0.8480		0.70 [0.33, 1.47], 0.3427	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2646		-0.01 [-0.15, 0.13], 0.8491		-0.05 [-0.15, 0.06], 0.3568	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.4851		0.7103		0.8532	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	19/73 (26.0)	8/36 (22.2)	15/77 (19.5)	6/29 (20.7)	34/150 (22.7)	14/65 (21.5)
RR [95%-CI]; p-value	1.17 [0.57, 2.41], 0.6684		0.94 [0.40, 2.19], 0.8889		1.05 [0.61, 1.82], 0.8557	
OR [95%-CI]; p-value	1.23 [0.48, 3.16], 0.6651		0.93 [0.32, 2.68], 0.8893		1.07 [0.53, 2.16], 0.8552	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6591		-0.01 [-0.18, 0.16], 0.8904		0.01 [-0.11, 0.13], 0.8542	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	19/68 (27.9)	12/36 (33.3)	18/67 (26.9)	10/43 (23.3)	37/135 (27.4)	22/79 (27.8)
RR [95%-CI]; p-value	0.84 [0.46, 1.53], 0.5639		1.16 [0.59, 2.26], 0.6736		0.98 [0.63, 1.54], 0.9445	
OR [95%-CI]; p-value	0.78 [0.32, 1.86], 0.5674		1.21 [0.50, 2.95], 0.6715		0.98 [0.53, 1.82], 0.9445	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.13], 0.5726		0.04 [-0.13, 0.20], 0.6680		-0.00 [-0.13, 0.12], 0.9446	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.9043		0.4341		0.5118	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	3/36 (8.3)	6/77 (7.8)	2/29 (6.9)	16/150 (10.7)	5/65 (7.7)
RR [95%-CI]; p-value	1.64 [0.48, 5.61], 0.4272		1.13 [0.24, 5.28], 0.8767		1.39 [0.53, 3.63], 0.5050	
OR [95%-CI]; p-value	1.75 [0.45, 6.78], 0.4163		1.14 [0.22, 6.00], 0.8763		1.43 [0.50, 4.09], 0.4999	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3804		0.01 [-0.10, 0.12], 0.8732		0.03 [-0.05, 0.11], 0.4742	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	2/36 (5.6)	5/67 (7.5)	1/43 (2.3)	12/135 (8.9)	3/79 (3.8)
RR [95%-CI]; p-value	1.85 [0.41, 8.46], 0.4260		3.21 [0.39, 26.54], 0.2794		2.34 [0.68, 8.04], 0.1769	
OR [95%-CI]; p-value	1.95 [0.38, 9.92], 0.4135		3.39 [0.38, 30.04], 0.2470		2.47 [0.68, 9.04], 0.1592	
RD [95%-CI]; p-value	0.05 [-0.06, 0.15], 0.3718		0.05 [-0.03, 0.13], 0.1932		0.05 [-0.01, 0.11], 0.1183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2208		0.4662		0.1763	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	11/73 (15.1)	4/36 (11.1)	10/77 (13.0)	3/29 (10.3)	21/150 (14.0)	7/65 (10.8)
RR [95%-CI]; p-value	1.36 [0.46, 3.96], 0.5777		1.26 [0.37, 4.24], 0.7142		1.30 [0.58, 2.91], 0.5226	
OR [95%-CI]; p-value	1.42 [0.42, 4.81], 0.5727		1.29 [0.33, 5.08], 0.7116		1.35 [0.54, 3.35], 0.5180	
RD [95%-CI]; p-value	0.04 [-0.09, 0.17], 0.5551		0.03 [-0.11, 0.16], 0.6989		0.03 [-0.06, 0.13], 0.4988	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	4/67 (6.0)	4/43 (9.3)	10/135 (7.4)	10/79 (12.7)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.17, 2.43], 0.5140		0.59 [0.25, 1.34], 0.2065	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.62 [0.15, 2.62], 0.5114		0.55 [0.22, 1.39], 0.2028	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.03 [-0.14, 0.07], 0.5289		-0.05 [-0.14, 0.03], 0.2293	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.8092		0.7112		0.9625	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	16/73 (21.9)	11/36 (30.6)	10/77 (13.0)	3/29 (10.3)	26/150 (17.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.72 [0.37, 1.38], 0.3207		1.26 [0.37, 4.24], 0.7142		0.80 [0.45, 1.44], 0.4636	
OR [95%-CI]; p-value	0.64 [0.26, 1.57], 0.3258		1.29 [0.33, 5.08], 0.7116		0.76 [0.37, 1.58], 0.4668	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3413		0.03 [-0.11, 0.16], 0.6989		-0.04 [-0.16, 0.07], 0.4806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	12/68 (17.6)	10/36 (27.8)	15/67 (22.4)	10/43 (23.3)	27/135 (20.0)	20/79 (25.3)
RR [95%-CI]; p-value	0.64 [0.30, 1.33], 0.2267		0.96 [0.48, 1.94], 0.9155		0.79 [0.48, 1.31], 0.3624	
OR [95%-CI]; p-value	0.56 [0.21, 1.45], 0.2288		0.95 [0.38, 2.37], 0.9156		0.74 [0.38, 1.43], 0.3646	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.07], 0.2486		-0.01 [-0.17, 0.15], 0.9158		-0.05 [-0.17, 0.06], 0.3741	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4955		0.0291		0.0732	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	15/73 (20.5)	12/36 (33.3)	14/77 (18.2)	2/29 (6.9)	29/150 (19.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.62 [0.32, 1.18], 0.1419		2.64 [0.64, 10.89], 0.1805		0.90 [0.51, 1.58], 0.7092	
OR [95%-CI]; p-value	0.52 [0.21, 1.27], 0.1459		3.00 [0.64, 14.12], 0.1479		0.87 [0.43, 1.79], 0.7105	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1632		0.11 [-0.01, 0.24], 0.0797		-0.02 [-0.14, 0.10], 0.7147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	11/36 (30.6)	8/67 (11.9)	12/43 (27.9)	17/135 (12.6)	23/79 (29.1)
RR [95%-CI]; p-value	0.43 [0.20, 0.95], 0.0362		0.43 [0.19, 0.96], 0.0396		0.43 [0.25, 0.76], 0.0035	
OR [95%-CI]; p-value	0.35 [0.13, 0.94], 0.0330		0.35 [0.13, 0.95], 0.0341		0.35 [0.17, 0.71], 0.0028	
RD [95%-CI]; p-value	-0.17 [-0.34, -0.00], 0.0467		-0.16 [-0.31, -0.00], 0.0434		-0.17 [-0.28, -0.05], 0.0048	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.7633		0.0722		0.2939	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	7/36 (19.4)	13/77 (16.9)	1/29 (3.4)	19/150 (12.7)	8/65 (12.3)
RR [95%-CI]; p-value	0.42 [0.15, 1.17], 0.0963		4.90 [0.67, 35.77], 0.1175		1.03 [0.48, 2.23], 0.9419	
OR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0890		5.69 [0.71, 45.61], 0.0686		1.03 [0.43, 2.50], 0.9418	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.03], 0.1261		0.13 [0.03, 0.24], 0.0137		0.00 [-0.09, 0.10], 0.9416	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	7/67 (10.4)	7/43 (16.3)	13/135 (9.6)	13/79 (16.5)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.24, 1.70], 0.3727		0.59 [0.29, 1.20], 0.1429	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.60 [0.19, 1.85], 0.3706		0.54 [0.24, 1.23], 0.1402	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.06 [-0.19, 0.07], 0.3882		-0.07 [-0.16, 0.03], 0.1622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7911		0.5869		0.9653	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	9/77 (11.7)	2/29 (6.9)	19/150 (12.7)	9/65 (13.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		1.69 [0.39, 7.38], 0.4822		0.91 [0.44, 1.91], 0.8130	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		1.79 [0.36, 8.81], 0.4708		0.90 [0.38, 2.12], 0.8134	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		0.05 [-0.07, 0.16], 0.4216		-0.01 [-0.11, 0.09], 0.8161	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	8/67 (11.9)	5/43 (11.6)	16/135 (11.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		1.03 [0.36, 2.93], 0.9605		0.94 [0.45, 1.96], 0.8615	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		1.03 [0.31, 3.39], 0.9605		0.93 [0.40, 2.16], 0.8617	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		0.00 [-0.12, 0.13], 0.9604		-0.01 [-0.10, 0.08], 0.8627	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.1437		0.3849		0.0542	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	1/36 (2.8)	10/77 (13.0)	2/29 (6.9)	14/150 (9.3)	3/65 (4.6)
RR [95%-CI]; p-value	1.97 [0.23, 17.01], 0.5366		1.88 [0.44, 8.08], 0.3945		2.02 [0.60, 6.80], 0.2550	
OR [95%-CI]; p-value	2.03 [0.22, 18.85], 0.5260		2.01 [0.41, 9.81], 0.3776		2.13 [0.59, 7.67], 0.2390	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.4795		0.06 [-0.06, 0.18], 0.3155		0.05 [-0.02, 0.12], 0.1806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	5/68 (7.4)	8/36 (22.2)	5/67 (7.5)	4/43 (9.3)	10/135 (7.4)	12/79 (15.2)
RR [95%-CI]; p-value	0.33 [0.12, 0.94], 0.0375		0.80 [0.23, 2.82], 0.7313		0.49 [0.22, 1.08], 0.0755	
OR [95%-CI]; p-value	0.28 [0.08, 0.92], 0.0292		0.79 [0.20, 3.11], 0.7312		0.45 [0.18, 1.09], 0.0704	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0509		-0.02 [-0.13, 0.09], 0.7367		-0.08 [-0.17, 0.01], 0.0924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9813		0.3475		0.5539	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	7/73 (9.6)	4/36 (11.1)	7/77 (9.1)	2/29 (6.9)	14/150 (9.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.86 [0.27, 2.76], 0.8037		1.32 [0.29, 5.98], 0.7203		1.01 [0.41, 2.51], 0.9810	
OR [95%-CI]; p-value	0.85 [0.23, 3.11], 0.8040		1.35 [0.26, 6.91], 0.7179		1.01 [0.37, 2.76], 0.9810	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8082		0.02 [-0.09, 0.13], 0.7019		0.00 [-0.08, 0.09], 0.9810	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	4/67 (6.0)	5/43 (11.6)	12/135 (8.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		0.51 [0.15, 1.81], 0.2989		0.70 [0.32, 1.55], 0.3816	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		0.48 [0.12, 1.91], 0.2908		0.67 [0.28, 1.64], 0.3809	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		-0.06 [-0.17, 0.05], 0.3193		-0.04 [-0.13, 0.05], 0.3992	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.3.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4447		0.8054		0.4238	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	2/73 (2.7)	6/36 (16.7)	3/77 (3.9)	0/29 (0.0)	5/150 (3.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.16 [0.03, 0.77], 0.0224		2.30 [0.12, 44.52], 0.5820		0.36 [0.11, 1.14], 0.0827	
OR [95%-CI]; p-value	0.14 [0.03, 0.74], 0.0087		2.35 [0.11, 48.40], 0.5685		0.34 [0.10, 1.15], 0.0715	
RD [95%-CI]; p-value	-0.14 [-0.27, -0.01], 0.0321		0.02 [-0.04, 0.09], 0.4972		-0.06 [-0.13, 0.02], 0.1283	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	6/36 (16.7)	3/67 (4.5)	0/43 (0.0)	7/135 (5.2)	6/79 (7.6)
RR [95%-CI]; p-value	0.35 [0.11, 1.17], 0.0887		3.90 [0.20, 75.89], 0.3694		0.68 [0.24, 1.96], 0.4781	
OR [95%-CI]; p-value	0.31 [0.08, 1.19], 0.0759		4.03 [0.20, 82.50], 0.3291		0.67 [0.22, 2.05], 0.4764	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1146		0.03 [-0.03, 0.09], 0.2671		-0.02 [-0.09, 0.05], 0.4959	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_3_m_pt_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.3.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0825		0.8341		0.3071	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	4/36 (11.1)	2/77 (2.6)	0/29 (0.0)	8/150 (5.3)	4/65 (6.2)
RR [95%-CI]; p-value	0.74 [0.22, 2.46], 0.6226		1.53 [0.07, 33.00], 0.7852		0.87 [0.27, 2.78], 0.8097	
OR [95%-CI]; p-value	0.72 [0.19, 2.72], 0.6228		1.55 [0.07, 35.32], 0.7831		0.86 [0.25, 2.96], 0.8098	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.09], 0.6379		0.01 [-0.05, 0.07], 0.7627		-0.01 [-0.08, 0.06], 0.8147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	1/68 (1.5)	6/36 (16.7)	5/67 (7.5)	3/43 (7.0)	6/135 (4.4)	9/79 (11.4)
RR [95%-CI]; p-value	0.09 [0.01, 0.70], 0.0220		1.07 [0.27, 4.25], 0.9238		0.39 [0.14, 1.06], 0.0637	
OR [95%-CI]; p-value	0.07 [0.01, 0.65], 0.0033		1.08 [0.24, 4.75], 0.9237		0.36 [0.12, 1.06], 0.0547	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.03], 0.0172		0.00 [-0.09, 0.10], 0.9232		-0.07 [-0.15, 0.01], 0.0817	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_3_m_pt_ae10pct_wt.sas using SAS 9.4

Table 12.4.8.1.1.s3
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9364		0.9529		0.6861	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	3/73 (4.1)	1/36 (2.8)	1/77 (1.3)	0/29 (0.0)	4/150 (2.7)	1/65 (1.5)
RR [95%-CI]; p-value	1.48 [0.16, 13.73], 0.7304		0.77 [0.03, 22.24], 0.8769		1.73 [0.20, 15.21], 0.6196	
OR [95%-CI]; p-value	1.50 [0.15, 14.95], 0.7280		0.76 [0.02, 23.37], 0.8766		1.75 [0.19, 16.00], 0.6142	
RD [95%-CI]; p-value	0.01 [-0.06, 0.08], 0.7108		-0.00 [-0.06, 0.05], 0.8835		0.01 [-0.03, 0.05], 0.5756	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	5/68 (7.4)	2/36 (5.6)	4/67 (6.0)	3/43 (7.0)	9/135 (6.7)	5/79 (6.3)
RR [95%-CI]; p-value	1.32 [0.27, 6.49], 0.7296		0.86 [0.20, 3.64], 0.8329		1.05 [0.37, 3.03], 0.9233	
OR [95%-CI]; p-value	1.35 [0.25, 7.33], 0.7278		0.85 [0.18, 3.98], 0.8329		1.06 [0.34, 3.27], 0.9232	
RD [95%-CI]; p-value	0.02 [-0.08, 0.12], 0.7170		-0.01 [-0.11, 0.08], 0.8354		0.00 [-0.06, 0.07], 0.9227	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_8_1_1_m_soc_sae5pct_wt.sas using SAS 9.4

Table 12.4.8.1.2.s3
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_8_1_2_m_pt_sae5pct_wt.sas using SAS 9.4

Table 12.4.5.1.1.s3
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_5_1_1_m_soc_aeg35pct_wt.sas using SAS 9.4

Table 12.4.5.1.2.s3
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_5_1_2_m_pt_aeg35pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6190		0.7629		0.6433	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	3/36 (8.3)	5/77 (6.5)	1/29 (3.4)	10/150 (6.7)	4/65 (6.2)
RR [95%-CI]; p-value	0.82 [0.21, 3.25], 0.7798		1.88 [0.23, 15.44], 0.5555		1.08 [0.35, 3.33], 0.8888	
OR [95%-CI]; p-value	0.81 [0.18, 3.59], 0.7799		1.94 [0.22, 17.39], 0.5453		1.09 [0.33, 3.61], 0.8887	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.09], 0.7863		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.07, 0.08], 0.8870	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	6/67 (9.0)	3/43 (7.0)	12/135 (8.9)	9/79 (11.4)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		1.28 [0.34, 4.86], 0.7133		0.78 [0.34, 1.77], 0.5524	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		1.31 [0.31, 5.55], 0.7118		0.76 [0.30, 1.89], 0.5525	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		0.02 [-0.08, 0.12], 0.7047		-0.03 [-0.11, 0.06], 0.5634	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1702		0.9337		0.6054	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	18/73 (24.7)	9/36 (25.0)	11/77 (14.3)	2/29 (6.9)	29/150 (19.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.99 [0.49, 1.97], 0.9689		2.07 [0.49, 8.79], 0.3232		1.14 [0.61, 2.15], 0.6787	
OR [95%-CI]; p-value	0.98 [0.39, 2.47], 0.9689		2.25 [0.47, 10.83], 0.3012		1.18 [0.55, 2.53], 0.6766	
RD [95%-CI]; p-value	-0.00 [-0.18, 0.17], 0.9690		0.07 [-0.05, 0.19], 0.2309		0.02 [-0.09, 0.14], 0.6702	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	10/68 (14.7)	11/36 (30.6)	15/67 (22.4)	5/43 (11.6)	25/135 (18.5)	16/79 (20.3)
RR [95%-CI]; p-value	0.48 [0.23, 1.02], 0.0577		1.93 [0.75, 4.91], 0.1705		0.91 [0.52, 1.61], 0.7551	
OR [95%-CI]; p-value	0.39 [0.15, 1.04], 0.0554		2.19 [0.73, 6.55], 0.1534		0.89 [0.44, 1.80], 0.7557	
RD [95%-CI]; p-value	-0.16 [-0.33, 0.01], 0.0716		0.11 [-0.03, 0.25], 0.1274		-0.02 [-0.13, 0.09], 0.7577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7893		0.6563		0.8313	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	7/77 (9.1)	4/29 (13.8)	17/150 (11.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		0.66 [0.21, 2.09], 0.4781		0.67 [0.33, 1.35], 0.2618	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		0.63 [0.17, 2.32], 0.4791		0.63 [0.28, 1.43], 0.2634	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		-0.05 [-0.19, 0.09], 0.5133		-0.06 [-0.16, 0.05], 0.2936	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	8/36 (22.2)	10/67 (14.9)	7/43 (16.3)	19/135 (14.1)	15/79 (19.0)
RR [95%-CI]; p-value	0.60 [0.25, 1.41], 0.2389		0.92 [0.38, 2.23], 0.8478		0.74 [0.40, 1.37], 0.3418	
OR [95%-CI]; p-value	0.53 [0.19, 1.53], 0.2384		0.90 [0.32, 2.58], 0.8480		0.70 [0.33, 1.47], 0.3427	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2646		-0.01 [-0.15, 0.13], 0.8491		-0.05 [-0.15, 0.06], 0.3568	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.4851		0.7103		0.8532	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	19/73 (26.0)	8/36 (22.2)	15/77 (19.5)	6/29 (20.7)	34/150 (22.7)	14/65 (21.5)
RR [95%-CI]; p-value	1.17 [0.57, 2.41], 0.6684		0.94 [0.40, 2.19], 0.8889		1.05 [0.61, 1.82], 0.8557	
OR [95%-CI]; p-value	1.23 [0.48, 3.16], 0.6651		0.93 [0.32, 2.68], 0.8893		1.07 [0.53, 2.16], 0.8552	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6591		-0.01 [-0.18, 0.16], 0.8904		0.01 [-0.11, 0.13], 0.8542	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	19/68 (27.9)	12/36 (33.3)	18/67 (26.9)	10/43 (23.3)	37/135 (27.4)	22/79 (27.8)
RR [95%-CI]; p-value	0.84 [0.46, 1.53], 0.5639		1.16 [0.59, 2.26], 0.6736		0.98 [0.63, 1.54], 0.9445	
OR [95%-CI]; p-value	0.78 [0.32, 1.86], 0.5674		1.21 [0.50, 2.95], 0.6715		0.98 [0.53, 1.82], 0.9445	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.13], 0.5726		0.04 [-0.13, 0.20], 0.6680		-0.00 [-0.13, 0.12], 0.9446	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.9043		0.4341		0.5118	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	3/36 (8.3)	6/77 (7.8)	2/29 (6.9)	16/150 (10.7)	5/65 (7.7)
RR [95%-CI]; p-value	1.64 [0.48, 5.61], 0.4272		1.13 [0.24, 5.28], 0.8767		1.39 [0.53, 3.63], 0.5050	
OR [95%-CI]; p-value	1.75 [0.45, 6.78], 0.4163		1.14 [0.22, 6.00], 0.8763		1.43 [0.50, 4.09], 0.4999	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3804		0.01 [-0.10, 0.12], 0.8732		0.03 [-0.05, 0.11], 0.4742	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	2/36 (5.6)	5/67 (7.5)	1/43 (2.3)	12/135 (8.9)	3/79 (3.8)
RR [95%-CI]; p-value	1.85 [0.41, 8.46], 0.4260		3.21 [0.39, 26.54], 0.2794		2.34 [0.68, 8.04], 0.1769	
OR [95%-CI]; p-value	1.95 [0.38, 9.92], 0.4135		3.39 [0.38, 30.04], 0.2470		2.47 [0.68, 9.04], 0.1592	
RD [95%-CI]; p-value	0.05 [-0.06, 0.15], 0.3718		0.05 [-0.03, 0.13], 0.1932		0.05 [-0.01, 0.11], 0.1183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2208		0.4662		0.1763	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	11/73 (15.1)	4/36 (11.1)	10/77 (13.0)	3/29 (10.3)	21/150 (14.0)	7/65 (10.8)
RR [95%-CI]; p-value	1.36 [0.46, 3.96], 0.5777		1.26 [0.37, 4.24], 0.7142		1.30 [0.58, 2.91], 0.5226	
OR [95%-CI]; p-value	1.42 [0.42, 4.81], 0.5727		1.29 [0.33, 5.08], 0.7116		1.35 [0.54, 3.35], 0.5180	
RD [95%-CI]; p-value	0.04 [-0.09, 0.17], 0.5551		0.03 [-0.11, 0.16], 0.6989		0.03 [-0.06, 0.13], 0.4988	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	4/67 (6.0)	4/43 (9.3)	10/135 (7.4)	10/79 (12.7)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.17, 2.43], 0.5140		0.59 [0.25, 1.34], 0.2065	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.62 [0.15, 2.62], 0.5114		0.55 [0.22, 1.39], 0.2028	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.03 [-0.14, 0.07], 0.5289		-0.05 [-0.14, 0.03], 0.2293	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.8092		0.7112		0.9625	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	16/73 (21.9)	11/36 (30.6)	10/77 (13.0)	3/29 (10.3)	26/150 (17.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.72 [0.37, 1.38], 0.3207		1.26 [0.37, 4.24], 0.7142		0.80 [0.45, 1.44], 0.4636	
OR [95%-CI]; p-value	0.64 [0.26, 1.57], 0.3258		1.29 [0.33, 5.08], 0.7116		0.76 [0.37, 1.58], 0.4668	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3413		0.03 [-0.11, 0.16], 0.6989		-0.04 [-0.16, 0.07], 0.4806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	12/68 (17.6)	10/36 (27.8)	15/67 (22.4)	10/43 (23.3)	27/135 (20.0)	20/79 (25.3)
RR [95%-CI]; p-value	0.64 [0.30, 1.33], 0.2267		0.96 [0.48, 1.94], 0.9155		0.79 [0.48, 1.31], 0.3624	
OR [95%-CI]; p-value	0.56 [0.21, 1.45], 0.2288		0.95 [0.38, 2.37], 0.9156		0.74 [0.38, 1.43], 0.3646	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.07], 0.2486		-0.01 [-0.17, 0.15], 0.9158		-0.05 [-0.17, 0.06], 0.3741	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4955		0.0291		0.0732	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	15/73 (20.5)	12/36 (33.3)	14/77 (18.2)	2/29 (6.9)	29/150 (19.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.62 [0.32, 1.18], 0.1419		2.64 [0.64, 10.89], 0.1805		0.90 [0.51, 1.58], 0.7092	
OR [95%-CI]; p-value	0.52 [0.21, 1.27], 0.1459		3.00 [0.64, 14.12], 0.1479		0.87 [0.43, 1.79], 0.7105	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1632		0.11 [-0.01, 0.24], 0.0797		-0.02 [-0.14, 0.10], 0.7147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	11/36 (30.6)	8/67 (11.9)	12/43 (27.9)	17/135 (12.6)	23/79 (29.1)
RR [95%-CI]; p-value	0.43 [0.20, 0.95], 0.0362		0.43 [0.19, 0.96], 0.0396		0.43 [0.25, 0.76], 0.0035	
OR [95%-CI]; p-value	0.35 [0.13, 0.94], 0.0330		0.35 [0.13, 0.95], 0.0341		0.35 [0.17, 0.71], 0.0028	
RD [95%-CI]; p-value	-0.17 [-0.34, -0.00], 0.0467		-0.16 [-0.31, -0.00], 0.0434		-0.17 [-0.28, -0.05], 0.0048	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.7633		0.0722		0.2939	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	7/36 (19.4)	13/77 (16.9)	1/29 (3.4)	19/150 (12.7)	8/65 (12.3)
RR [95%-CI]; p-value	0.42 [0.15, 1.17], 0.0963		4.90 [0.67, 35.77], 0.1175		1.03 [0.48, 2.23], 0.9419	
OR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0890		5.69 [0.71, 45.61], 0.0686		1.03 [0.43, 2.50], 0.9418	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.03], 0.1261		0.13 [0.03, 0.24], 0.0137		0.00 [-0.09, 0.10], 0.9416	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	7/67 (10.4)	7/43 (16.3)	13/135 (9.6)	13/79 (16.5)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.24, 1.70], 0.3727		0.59 [0.29, 1.20], 0.1429	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.60 [0.19, 1.85], 0.3706		0.54 [0.24, 1.23], 0.1402	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.06 [-0.19, 0.07], 0.3882		-0.07 [-0.16, 0.03], 0.1622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.3783		0.6938		0.3435	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	9/73 (12.3)	3/36 (8.3)	6/77 (7.8)	2/29 (6.9)	15/150 (10.0)	5/65 (7.7)
RR [95%-CI]; p-value	1.48 [0.43, 5.13], 0.5372		1.13 [0.24, 5.28], 0.8767		1.30 [0.49, 3.43], 0.5958	
OR [95%-CI]; p-value	1.55 [0.39, 6.10], 0.5308		1.14 [0.22, 6.00], 0.8763		1.33 [0.46, 3.84], 0.5926	
RD [95%-CI]; p-value	0.04 [-0.08, 0.16], 0.5056		0.01 [-0.10, 0.12], 0.8732		0.02 [-0.06, 0.10], 0.5748	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	2/36 (5.6)	6/67 (9.0)	5/43 (11.6)	8/135 (5.9)	7/79 (8.9)
RR [95%-CI]; p-value	0.53 [0.08, 3.60], 0.5157		0.77 [0.25, 2.37], 0.6486		0.67 [0.25, 1.77], 0.4190	
OR [95%-CI]; p-value	0.52 [0.07, 3.82], 0.5095		0.75 [0.21, 2.62], 0.6484		0.65 [0.23, 1.86], 0.4171	
RD [95%-CI]; p-value	-0.03 [-0.11, 0.06], 0.5462		-0.03 [-0.14, 0.09], 0.6563		-0.03 [-0.10, 0.04], 0.4385	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7911		0.5869		0.9653	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	9/77 (11.7)	2/29 (6.9)	19/150 (12.7)	9/65 (13.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		1.69 [0.39, 7.38], 0.4822		0.91 [0.44, 1.91], 0.8130	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		1.79 [0.36, 8.81], 0.4708		0.90 [0.38, 2.12], 0.8134	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		0.05 [-0.07, 0.16], 0.4216		-0.01 [-0.11, 0.09], 0.8161	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	8/67 (11.9)	5/43 (11.6)	16/135 (11.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		1.03 [0.36, 2.93], 0.9605		0.94 [0.45, 1.96], 0.8615	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		1.03 [0.31, 3.39], 0.9605		0.93 [0.40, 2.16], 0.8617	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		0.00 [-0.12, 0.13], 0.9604		-0.01 [-0.10, 0.08], 0.8627	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.1437		0.3849		0.0542	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	1/36 (2.8)	10/77 (13.0)	2/29 (6.9)	14/150 (9.3)	3/65 (4.6)
RR [95%-CI]; p-value	1.97 [0.23, 17.01], 0.5366		1.88 [0.44, 8.08], 0.3945		2.02 [0.60, 6.80], 0.2550	
OR [95%-CI]; p-value	2.03 [0.22, 18.85], 0.5260		2.01 [0.41, 9.81], 0.3776		2.13 [0.59, 7.67], 0.2390	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.4795		0.06 [-0.06, 0.18], 0.3155		0.05 [-0.02, 0.12], 0.1806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	5/68 (7.4)	8/36 (22.2)	5/67 (7.5)	4/43 (9.3)	10/135 (7.4)	12/79 (15.2)
RR [95%-CI]; p-value	0.33 [0.12, 0.94], 0.0375		0.80 [0.23, 2.82], 0.7313		0.49 [0.22, 1.08], 0.0755	
OR [95%-CI]; p-value	0.28 [0.08, 0.92], 0.0292		0.79 [0.20, 3.11], 0.7312		0.45 [0.18, 1.09], 0.0704	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0509		-0.02 [-0.13, 0.09], 0.7367		-0.08 [-0.17, 0.01], 0.0924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9813		0.3475		0.5539	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	7/73 (9.6)	4/36 (11.1)	7/77 (9.1)	2/29 (6.9)	14/150 (9.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.86 [0.27, 2.76], 0.8037		1.32 [0.29, 5.98], 0.7203		1.01 [0.41, 2.51], 0.9810	
OR [95%-CI]; p-value	0.85 [0.23, 3.11], 0.8040		1.35 [0.26, 6.91], 0.7179		1.01 [0.37, 2.76], 0.9810	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8082		0.02 [-0.09, 0.13], 0.7019		0.00 [-0.08, 0.09], 0.9810	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	4/67 (6.0)	5/43 (11.6)	12/135 (8.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		0.51 [0.15, 1.81], 0.2989		0.70 [0.32, 1.55], 0.3816	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		0.48 [0.12, 1.91], 0.2908		0.67 [0.28, 1.64], 0.3809	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		-0.06 [-0.17, 0.05], 0.3193		-0.04 [-0.13, 0.05], 0.3992	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.4.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4447		0.8054		0.4238	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	2/73 (2.7)	6/36 (16.7)	3/77 (3.9)	0/29 (0.0)	5/150 (3.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.16 [0.03, 0.77], 0.0224		2.30 [0.12, 44.52], 0.5820		0.36 [0.11, 1.14], 0.0827	
OR [95%-CI]; p-value	0.14 [0.03, 0.74], 0.0087		2.35 [0.11, 48.40], 0.5685		0.34 [0.10, 1.15], 0.0715	
RD [95%-CI]; p-value	-0.14 [-0.27, -0.01], 0.0321		0.02 [-0.04, 0.09], 0.4972		-0.06 [-0.13, 0.02], 0.1283	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	6/36 (16.7)	3/67 (4.5)	0/43 (0.0)	7/135 (5.2)	6/79 (7.6)
RR [95%-CI]; p-value	0.35 [0.11, 1.17], 0.0887		3.90 [0.20, 75.89], 0.3694		0.68 [0.24, 1.96], 0.4781	
OR [95%-CI]; p-value	0.31 [0.08, 1.19], 0.0759		4.03 [0.20, 82.50], 0.3291		0.67 [0.22, 2.05], 0.4764	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1146		0.03 [-0.03, 0.09], 0.2671		-0.02 [-0.09, 0.05], 0.4959	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_4_m_pt_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.4.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0825		0.8341		0.3071	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	4/36 (11.1)	2/77 (2.6)	0/29 (0.0)	8/150 (5.3)	4/65 (6.2)
RR [95%-CI]; p-value	0.74 [0.22, 2.46], 0.6226		1.53 [0.07, 33.00], 0.7852		0.87 [0.27, 2.78], 0.8097	
OR [95%-CI]; p-value	0.72 [0.19, 2.72], 0.6228		1.55 [0.07, 35.32], 0.7831		0.86 [0.25, 2.96], 0.8098	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.09], 0.6379		0.01 [-0.05, 0.07], 0.7627		-0.01 [-0.08, 0.06], 0.8147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	1/68 (1.5)	6/36 (16.7)	5/67 (7.5)	3/43 (7.0)	6/135 (4.4)	9/79 (11.4)
RR [95%-CI]; p-value	0.09 [0.01, 0.70], 0.0220		1.07 [0.27, 4.25], 0.9238		0.39 [0.14, 1.06], 0.0637	
OR [95%-CI]; p-value	0.07 [0.01, 0.65], 0.0033		1.08 [0.24, 4.75], 0.9237		0.36 [0.12, 1.06], 0.0547	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.03], 0.0172		0.00 [-0.09, 0.10], 0.9232		-0.07 [-0.15, 0.01], 0.0817	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_4_m_pt_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.4.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.9476		0.2163		0.3945	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	2/36 (5.6)	5/77 (6.5)	1/29 (3.4)	9/150 (6.0)	3/65 (4.6)
RR [95%-CI]; p-value	0.99 [0.19, 5.13], 0.9869		1.88 [0.23, 15.44], 0.5555		1.30 [0.36, 4.65], 0.6864	
OR [95%-CI]; p-value	0.99 [0.17, 5.65], 0.9869		1.94 [0.22, 17.39], 0.5453		1.32 [0.35, 5.04], 0.6846	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.09], 0.9870		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.05, 0.08], 0.6696	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	3/36 (8.3)	3/67 (4.5)	5/43 (11.6)	9/135 (6.7)	8/79 (10.1)
RR [95%-CI]; p-value	1.06 [0.28, 3.99], 0.9327		0.39 [0.10, 1.53], 0.1750		0.66 [0.26, 1.64], 0.3684	
OR [95%-CI]; p-value	1.06 [0.25, 4.53], 0.9326		0.36 [0.08, 1.58], 0.1588		0.63 [0.23, 1.72], 0.3664	
RD [95%-CI]; p-value	0.00 [-0.11, 0.12], 0.9320		-0.07 [-0.18, 0.04], 0.1938		-0.03 [-0.11, 0.04], 0.3890	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_4_m_pt_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.7820		0.5567		0.4248	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	11/73 (15.1)	2/36 (5.6)	5/77 (6.5)	2/29 (6.9)	16/150 (10.7)	4/65 (6.2)
RR [95%-CI]; p-value	2.71 [0.63, 11.60], 0.1783		0.94 [0.19, 4.59], 0.9406		1.73 [0.60, 4.98], 0.3074	
OR [95%-CI]; p-value	3.02 [0.63, 14.41], 0.1495		0.94 [0.17, 5.12], 0.9406		1.82 [0.58, 5.67], 0.2954	
RD [95%-CI]; p-value	0.10 [-0.02, 0.21], 0.0932		-0.00 [-0.11, 0.10], 0.9414		0.05 [-0.03, 0.12], 0.2476	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	0/36 (0.0)	4/67 (6.0)	5/43 (11.6)	8/135 (5.9)	5/79 (6.3)
RR [95%-CI]; p-value	4.29 [0.23, 79.01], 0.3267		0.51 [0.15, 1.81], 0.2989		0.94 [0.32, 2.76], 0.9051	
OR [95%-CI]; p-value	4.50 [0.23, 87.55], 0.2787		0.48 [0.12, 1.91], 0.2908		0.93 [0.29, 2.95], 0.9051	
RD [95%-CI]; p-value	0.05 [-0.02, 0.11], 0.1898		-0.06 [-0.17, 0.05], 0.3193		-0.00 [-0.07, 0.06], 0.9059	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9767		0.7182		0.6045	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	1/73 (1.4)	0/36 (0.0)	1/77 (1.3)	0/29 (0.0)	2/150 (1.3)	0/65 (0.0)
RR [95%-CI]; p-value	1.00 [0.03, 29.12], 1.0000		0.77 [0.03, 22.24], 0.8769		1.75 [0.08, 38.21], 0.7231	
OR [95%-CI]; p-value	1.00 [0.03, 30.52], 1.0000		0.76 [0.02, 23.37], 0.8766		1.76 [0.08, 39.49], 0.7193	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 1.0000		-0.00 [-0.06, 0.05], 0.8835		0.01 [-0.02, 0.03], 0.6894	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	1/68 (1.5)	0/36 (0.0)	0/67 (0.0)	1/43 (2.3)	1/135 (0.7)	1/79 (1.3)
RR [95%-CI]; p-value	1.07 [0.04, 31.24], 0.9671		0.32 [0.01, 9.29], 0.5062		0.59 [0.04, 9.23], 0.7034	
OR [95%-CI]; p-value	1.07 [0.04, 32.81], 0.9671		0.31 [0.01, 9.55], 0.4827		0.58 [0.04, 9.44], 0.7001	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9667		-0.02 [-0.07, 0.03], 0.5301		-0.01 [-0.03, 0.02], 0.7188	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8743		0.8820		0.6319	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	2/36 (5.6)	4/77 (5.2)	2/29 (6.9)	14/150 (9.3)	4/65 (6.2)
RR [95%-CI]; p-value	2.47 [0.57, 10.67], 0.2272		0.75 [0.15, 3.89], 0.7353		1.52 [0.52, 4.43], 0.4465	
OR [95%-CI]; p-value	2.70 [0.56, 13.03], 0.2014		0.74 [0.13, 4.27], 0.7354		1.57 [0.50, 4.97], 0.4395	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1421		-0.02 [-0.12, 0.09], 0.7501		0.03 [-0.04, 0.11], 0.4042	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	3/68 (4.4)	0/36 (0.0)	4/67 (6.0)	4/43 (9.3)	7/135 (5.2)	4/79 (5.1)
RR [95%-CI]; p-value	3.22 [0.17, 62.57], 0.4397		0.64 [0.17, 2.43], 0.5140		1.02 [0.31, 3.39], 0.9689	
OR [95%-CI]; p-value	3.32 [0.16, 68.19], 0.4100		0.62 [0.15, 2.62], 0.5114		1.03 [0.29, 3.62], 0.9689	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3337		-0.03 [-0.14, 0.07], 0.5289		0.00 [-0.06, 0.06], 0.9688	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.9420		0.6109		0.8382	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	1/36 (2.8)	3/77 (3.9)	0/29 (0.0)	8/150 (5.3)	1/65 (1.5)
RR [95%-CI]; p-value	2.47 [0.30, 20.33], 0.4018		2.30 [0.12, 44.52], 0.5820		3.47 [0.44, 27.16], 0.2365	
OR [95%-CI]; p-value	2.57 [0.29, 22.89], 0.3807		2.35 [0.11, 48.40], 0.5685		3.61 [0.44, 29.44], 0.2019	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3124		0.02 [-0.04, 0.09], 0.4972		0.04 [-0.01, 0.08], 0.1118	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	0/36 (0.0)	0/67 (0.0)	0/43 (0.0)	2/135 (1.5)	0/79 (0.0)
RR [95%-CI]; p-value	2.15 [0.10, 46.38], 0.6260		NA		2.36 [0.11, 51.59], 0.5864	
OR [95%-CI]; p-value	2.18 [0.10, 49.68], 0.6163		NA		2.38 [0.11, 53.35], 0.5742	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5761		NA		0.01 [-0.02, 0.04], 0.5327	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8268		0.4665		0.5125	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	4/36 (11.1)	6/77 (7.8)	3/29 (10.3)	11/150 (7.3)	7/65 (10.8)
RR [95%-CI]; p-value	0.62 [0.18, 2.16], 0.4491		0.75 [0.20, 2.82], 0.6736		0.68 [0.28, 1.68], 0.4036	
OR [95%-CI]; p-value	0.59 [0.15, 2.34], 0.4471		0.73 [0.17, 3.14], 0.6743		0.66 [0.24, 1.78], 0.4035	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.08], 0.4786		-0.03 [-0.15, 0.10], 0.6913		-0.03 [-0.12, 0.05], 0.4343	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	5/36 (13.9)	7/67 (10.4)	3/43 (7.0)	14/135 (10.4)	8/79 (10.1)
RR [95%-CI]; p-value	0.74 [0.25, 2.17], 0.5847		1.50 [0.41, 5.48], 0.5418		1.02 [0.45, 2.33], 0.9548	
OR [95%-CI]; p-value	0.71 [0.21, 2.43], 0.5851		1.56 [0.38, 6.37], 0.5366		1.03 [0.41, 2.57], 0.9548	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.10], 0.5993		0.03 [-0.07, 0.14], 0.5196		0.00 [-0.08, 0.09], 0.9547	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.6016		0.5316		0.8734	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	2/73 (2.7)	0/36 (0.0)	2/77 (2.6)	1/29 (3.4)	4/150 (2.7)	1/65 (1.5)
RR [95%-CI]; p-value	2.00 [0.09, 43.23], 0.6585		0.75 [0.07, 7.99], 0.8141		1.73 [0.20, 15.21], 0.6196	
OR [95%-CI]; p-value	2.03 [0.09, 46.15], 0.6510		0.75 [0.07, 8.56], 0.8138		1.75 [0.19, 16.00], 0.6142	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.6134		-0.01 [-0.08, 0.07], 0.8248		0.01 [-0.03, 0.05], 0.5756	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	0/68 (0.0)	0/36 (0.0)	2/67 (3.0)	0/43 (0.0)	2/135 (1.5)	0/79 (0.0)
RR [95%-CI]; p-value	NA		2.60 [0.12, 56.25], 0.5430		2.36 [0.11, 51.59], 0.5864	
OR [95%-CI]; p-value	NA		2.65 [0.12, 60.10], 0.5261		2.38 [0.11, 53.35], 0.5742	
RD [95%-CI]; p-value	NA		0.02 [-0.03, 0.07], 0.4857		0.01 [-0.02, 0.04], 0.5327	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.4488		0.3474		0.2390	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	3/73 (4.1)	4/36 (11.1)	4/77 (5.2)	3/29 (10.3)	7/150 (4.7)	7/65 (10.8)
RR [95%-CI]; p-value	0.37 [0.09, 1.57], 0.1766		0.50 [0.12, 2.11], 0.3467		0.43 [0.16, 1.19], 0.1034	
OR [95%-CI]; p-value	0.34 [0.07, 1.62], 0.1608		0.47 [0.10, 2.27], 0.3412		0.41 [0.14, 1.21], 0.0958	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2217		-0.05 [-0.17, 0.07], 0.4058		-0.06 [-0.14, 0.02], 0.1475	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	5/36 (13.9)	6/67 (9.0)	3/43 (7.0)	13/135 (9.6)	8/79 (10.1)
RR [95%-CI]; p-value	0.74 [0.25, 2.17], 0.5847		1.28 [0.34, 4.86], 0.7133		0.95 [0.41, 2.19], 0.9061	
OR [95%-CI]; p-value	0.71 [0.21, 2.43], 0.5851		1.31 [0.31, 5.55], 0.7118		0.95 [0.37, 2.39], 0.9061	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.10], 0.5993		0.02 [-0.08, 0.12], 0.7047		-0.00 [-0.09, 0.08], 0.9067	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8780		0.6673		0.7463	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	3/73 (4.1)	0/36 (0.0)	3/77 (3.9)	1/29 (3.4)	6/150 (4.0)	1/65 (1.5)
RR [95%-CI]; p-value	3.00 [0.15, 58.32], 0.4681		1.13 [0.12, 10.43], 0.9143		2.60 [0.32, 21.17], 0.3718	
OR [95%-CI]; p-value	3.09 [0.15, 63.28], 0.4423		1.14 [0.11, 11.37], 0.9141		2.67 [0.31, 22.61], 0.3503	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3638		0.00 [-0.07, 0.08], 0.9118		0.02 [-0.02, 0.07], 0.2657	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	0/36 (0.0)	2/67 (3.0)	0/43 (0.0)	4/135 (3.0)	0/79 (0.0)
RR [95%-CI]; p-value	2.15 [0.10, 46.38], 0.6260		2.60 [0.12, 56.25], 0.5430		4.71 [0.25, 87.95], 0.2993	
OR [95%-CI]; p-value	2.18 [0.10, 49.68], 0.6163		2.65 [0.12, 60.10], 0.5261		4.82 [0.25, 92.47], 0.2493	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5761		0.02 [-0.03, 0.07], 0.4857		0.02 [-0.01, 0.06], 0.1717	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.6.s3
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.3308		0.8647		0.7277	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	13/73 (17.8)	7/36 (19.4)	12/77 (15.6)	3/29 (10.3)	25/150 (16.7)	10/65 (15.4)
RR [95%-CI]; p-value	0.92 [0.40, 2.10], 0.8351		1.51 [0.46, 4.96], 0.5000		1.08 [0.55, 2.12], 0.8157	
OR [95%-CI]; p-value	0.90 [0.32, 2.49], 0.8356		1.60 [0.42, 6.14], 0.4902		1.10 [0.49, 2.45], 0.8151	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8374		0.05 [-0.08, 0.19], 0.4545		0.01 [-0.09, 0.12], 0.8127	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	11/68 (16.2)	11/36 (30.6)	16/67 (23.9)	6/43 (14.0)	27/135 (20.0)	17/79 (21.5)
RR [95%-CI]; p-value	0.53 [0.25, 1.10], 0.0884		1.71 [0.73, 4.03], 0.2189		0.93 [0.54, 1.59], 0.7903	
OR [95%-CI]; p-value	0.44 [0.17, 1.14], 0.0876		1.93 [0.69, 5.42], 0.2040		0.91 [0.46, 1.80], 0.7908	
RD [95%-CI]; p-value	-0.14 [-0.32, 0.03], 0.1055		0.10 [-0.05, 0.24], 0.1809		-0.02 [-0.13, 0.10], 0.7922	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_6_m_pt_adr_wt.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.0911		0.6196		0.1952	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	61/85 (71.8)	34/48 (70.8)	66/98 (67.3)	29/46 (63.0)	127/183 (69.4)	63/94 (67.0)
RR [95%-CI]; p-value	1.01 [0.81, 1.27], 0.9095		1.07 [0.82, 1.39], 0.6196		1.04 [0.87, 1.23], 0.6901	
OR [95%-CI]; p-value	1.05 [0.48, 2.29], 0.9091		1.21 [0.58, 2.52], 0.6113		1.12 [0.66, 1.90], 0.6864	
RD [95%-CI]; p-value	0.01 [-0.15, 0.17], 0.9093		0.04 [-0.12, 0.21], 0.6147		0.02 [-0.09, 0.14], 0.6883	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	40/56 (71.4)	22/24 (91.7)	25/46 (54.3)	15/26 (57.7)	65/102 (63.7)	37/50 (74.0)
RR [95%-CI]; p-value	0.78 [0.63, 0.96], 0.0170		0.94 [0.62, 1.44], 0.7817		0.86 [0.69, 1.07], 0.1831	
OR [95%-CI]; p-value	0.23 [0.05, 1.08], 0.0470		0.87 [0.33, 2.30], 0.7838		0.62 [0.29, 1.31], 0.2053	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0143		-0.03 [-0.27, 0.20], 0.7832		-0.10 [-0.26, 0.05], 0.1889	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.9004		0.3586		0.2466	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	11/85 (12.9)	8/48 (16.7)	10/98 (10.2)	2/46 (4.3)	21/183 (11.5)	10/94 (10.6)
RR [95%-CI]; p-value	0.78 [0.34, 1.80], 0.5546		2.35 [0.54, 10.28], 0.2577		1.08 [0.53, 2.20], 0.8346	
OR [95%-CI]; p-value	0.74 [0.28, 2.00], 0.5554		2.50 [0.52, 11.91], 0.2358		1.09 [0.49, 2.42], 0.8343	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.09], 0.5663		0.06 [-0.03, 0.14], 0.1721		0.01 [-0.07, 0.09], 0.8325	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	6/56 (10.7)	3/24 (12.5)	9/46 (19.6)	0/26 (0.0)	15/102 (14.7)	3/50 (6.0)
RR [95%-CI]; p-value	0.86 [0.23, 3.15], 0.8163		10.37 [0.63, 171.78], 0.1025		2.45 [0.74, 8.08], 0.1406	
OR [95%-CI]; p-value	0.84 [0.19, 3.68], 0.8168		12.65 [0.70, 227.95], 0.0317		2.70 [0.74, 9.81], 0.1186	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8215		0.18 [0.05, 0.30], 0.0059		0.09 [-0.01, 0.18], 0.0730	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.8363		0.6160		0.6665	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	4/48 (8.3)	5/98 (5.1)	4/46 (8.7)	15/183 (8.2)	8/94 (8.5)
RR [95%-CI]; p-value	1.41 [0.47, 4.26], 0.5405		0.59 [0.17, 2.08], 0.4096		0.96 [0.42, 2.19], 0.9285	
OR [95%-CI]; p-value	1.47 [0.43, 4.96], 0.5357		0.56 [0.14, 2.21], 0.4062		0.96 [0.39, 2.35], 0.9286	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5176		-0.04 [-0.13, 0.06], 0.4456		-0.00 [-0.07, 0.07], 0.9290	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	2/24 (8.3)	5/46 (10.9)	3/26 (11.5)	13/102 (12.7)	5/50 (10.0)
RR [95%-CI]; p-value	1.71 [0.39, 7.48], 0.4735		0.94 [0.24, 3.63], 0.9308		1.27 [0.48, 3.38], 0.6256	
OR [95%-CI]; p-value	1.83 [0.36, 9.35], 0.4607		0.93 [0.20, 4.27], 0.9309		1.31 [0.44, 3.92], 0.6226	
RD [95%-CI]; p-value	0.06 [-0.08, 0.20], 0.4166		-0.01 [-0.16, 0.15], 0.9314		0.03 [-0.08, 0.13], 0.6096	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.5806		0.5890		0.9904	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	18/85 (21.2)	7/48 (14.6)	13/98 (13.3)	7/46 (15.2)	31/183 (16.9)	14/94 (14.9)
RR [95%-CI]; p-value	1.45 [0.65, 3.23], 0.3597		0.87 [0.37, 2.04], 0.7514		1.14 [0.64, 2.03], 0.6636	
OR [95%-CI]; p-value	1.57 [0.61, 4.09], 0.3499		0.85 [0.32, 2.30], 0.7521		1.17 [0.59, 2.32], 0.6620	
RD [95%-CI]; p-value	0.07 [-0.07, 0.20], 0.3288		-0.02 [-0.14, 0.10], 0.7570		0.02 [-0.07, 0.11], 0.6565	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	12/56 (21.4)	5/24 (20.8)	9/46 (19.6)	4/26 (15.4)	21/102 (20.6)	9/50 (18.0)
RR [95%-CI]; p-value	1.03 [0.41, 2.60], 0.9525		1.27 [0.43, 3.73], 0.6612		1.14 [0.57, 2.31], 0.7083	
OR [95%-CI]; p-value	1.04 [0.32, 3.35], 0.9524		1.34 [0.37, 4.86], 0.6578		1.18 [0.50, 2.81], 0.7064	
RD [95%-CI]; p-value	0.01 [-0.19, 0.20], 0.9522		0.04 [-0.14, 0.22], 0.6488		0.03 [-0.11, 0.16], 0.7013	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.1480		0.2484		0.8388	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	11/85 (12.9)	2/48 (4.2)	7/98 (7.1)	3/46 (6.5)	18/183 (9.8)	5/94 (5.3)
RR [95%-CI]; p-value	3.11 [0.72, 13.43], 0.1293		1.10 [0.30, 4.04], 0.8914		1.85 [0.71, 4.83], 0.2090	
OR [95%-CI]; p-value	3.42 [0.72, 16.12], 0.1017		1.10 [0.27, 4.47], 0.8913		1.94 [0.70, 5.41], 0.1970	
RD [95%-CI]; p-value	0.09 [-0.00, 0.18], 0.0589		0.01 [-0.08, 0.09], 0.8896		0.05 [-0.02, 0.11], 0.1574	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	3/24 (12.5)	8/46 (17.4)	1/26 (3.8)	13/102 (12.7)	4/50 (8.0)
RR [95%-CI]; p-value	0.71 [0.19, 2.75], 0.6250		4.52 [0.60, 34.17], 0.1437		1.59 [0.55, 4.64], 0.3929	
OR [95%-CI]; p-value	0.69 [0.15, 3.13], 0.6256		5.26 [0.62, 44.70], 0.0951		1.68 [0.52, 5.44], 0.3832	
RD [95%-CI]; p-value	-0.04 [-0.19, 0.12], 0.6450		0.14 [0.00, 0.27], 0.0445		0.05 [-0.05, 0.15], 0.3485	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.2030		0.1741		0.8265	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	0/48 (0.0)	3/98 (3.1)	3/46 (6.5)	8/183 (4.4)	3/94 (3.2)
RR [95%-CI]; p-value	5.71 [0.32, 102.22], 0.2369		0.47 [0.10, 2.24], 0.3425		1.37 [0.37, 5.04], 0.6361	
OR [95%-CI]; p-value	6.00 [0.32, 112.26], 0.1750		0.45 [0.09, 2.33], 0.3326		1.39 [0.36, 5.35], 0.6339	
RD [95%-CI]; p-value	0.05 [-0.01, 0.11], 0.0984		-0.03 [-0.11, 0.04], 0.3911		0.01 [-0.03, 0.06], 0.6171	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	3/56 (5.4)	2/24 (8.3)	4/46 (8.7)	0/26 (0.0)	7/102 (6.9)	2/50 (4.0)
RR [95%-CI]; p-value	0.64 [0.11, 3.60], 0.6155		4.61 [0.25, 83.83], 0.3019		1.72 [0.37, 7.96], 0.4905	
OR [95%-CI]; p-value	0.62 [0.10, 3.99], 0.6143		4.95 [0.25, 97.54], 0.2472		1.77 [0.35, 8.84], 0.4823	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.10], 0.6416		0.07 [-0.03, 0.16], 0.1667		0.03 [-0.04, 0.10], 0.4433	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.9033		0.9223		0.7139	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	2/85 (2.4)	1/48 (2.1)	2/98 (2.0)	1/46 (2.2)	4/183 (2.2)	2/94 (2.1)
RR [95%-CI]; p-value	1.13 [0.11, 12.13], 0.9200		0.94 [0.09, 10.09], 0.9584		1.03 [0.19, 5.51], 0.9749	
OR [95%-CI]; p-value	1.13 [0.10, 12.83], 0.9199		0.94 [0.08, 10.61], 0.9584		1.03 [0.18, 5.72], 0.9749	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9186		-0.00 [-0.05, 0.05], 0.9589		0.00 [-0.04, 0.04], 0.9748	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
RR [95%-CI]; p-value	0.88 [0.03, 25.23], 0.9379		1.15 [0.04, 33.20], 0.9342		1.98 [0.09, 43.11], 0.6638	
OR [95%-CI]; p-value	0.87 [0.03, 26.91], 0.9379		1.16 [0.04, 35.64], 0.9341		2.00 [0.09, 45.18], 0.6568	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.06], 0.9395		0.00 [-0.06, 0.07], 0.9328		0.01 [-0.03, 0.05], 0.6197	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.0492		0.9491		0.2194	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	50/85 (58.8)	29/48 (60.4)	51/98 (52.0)	24/46 (52.2)	101/183 (55.2)	53/94 (56.4)
RR [95%-CI]; p-value	0.97 [0.73, 1.30], 0.8566		1.00 [0.71, 1.40], 0.9881		0.98 [0.79, 1.22], 0.8495	
OR [95%-CI]; p-value	0.94 [0.45, 1.93], 0.8574		0.99 [0.49, 2.01], 0.9881		0.95 [0.58, 1.57], 0.8501	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.16], 0.8571		-0.00 [-0.18, 0.17], 0.9881		-0.01 [-0.14, 0.11], 0.8499	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	32/56 (57.1)	21/24 (87.5)	19/46 (41.3)	11/26 (42.3)	51/102 (50.0)	32/50 (64.0)
RR [95%-CI]; p-value	0.65 [0.50, 0.86], 0.0022		0.98 [0.55, 1.72], 0.9337		0.78 [0.59, 1.04], 0.0889	
OR [95%-CI]; p-value	0.19 [0.05, 0.71], 0.0085		0.96 [0.36, 2.54], 0.9339		0.56 [0.28, 1.13], 0.1034	
RD [95%-CI]; p-value	-0.30 [-0.49, -0.12], 0.0013		-0.01 [-0.25, 0.23], 0.9340		-0.14 [-0.30, 0.02], 0.0957	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.7236		0.1835		0.3042	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	33/85 (38.8)	20/48 (41.7)	34/98 (34.7)	9/46 (19.6)	67/183 (36.6)	29/94 (30.9)
RR [95%-CI]; p-value	0.93 [0.61, 1.43], 0.7463		1.77 [0.93, 3.38], 0.0821		1.19 [0.83, 1.70], 0.3482	
OR [95%-CI]; p-value	0.89 [0.43, 1.83], 0.7477		2.18 [0.94, 5.05], 0.0644		1.29 [0.76, 2.20], 0.3401	
RD [95%-CI]; p-value	-0.03 [-0.20, 0.15], 0.7484		0.15 [0.00, 0.30], 0.0457		0.06 [-0.06, 0.17], 0.3328	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	17/56 (30.4)	9/24 (37.5)	15/46 (32.6)	9/26 (34.6)	32/102 (31.4)	18/50 (36.0)
RR [95%-CI]; p-value	0.81 [0.42, 1.55], 0.5248		0.94 [0.48, 1.84], 0.8617		0.87 [0.55, 1.39], 0.5644	
OR [95%-CI]; p-value	0.73 [0.27, 1.98], 0.5319		0.91 [0.33, 2.53], 0.8623		0.81 [0.40, 1.66], 0.5683	
RD [95%-CI]; p-value	-0.07 [-0.30, 0.16], 0.5393		-0.02 [-0.25, 0.21], 0.8628		-0.05 [-0.21, 0.11], 0.5724	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.8363		0.6160		0.6665	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	4/48 (8.3)	5/98 (5.1)	4/46 (8.7)	15/183 (8.2)	8/94 (8.5)
RR [95%-CI]; p-value	1.41 [0.47, 4.26], 0.5405		0.59 [0.17, 2.08], 0.4096		0.96 [0.42, 2.19], 0.9285	
OR [95%-CI]; p-value	1.47 [0.43, 4.96], 0.5357		0.56 [0.14, 2.21], 0.4062		0.96 [0.39, 2.35], 0.9286	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5176		-0.04 [-0.13, 0.06], 0.4456		-0.00 [-0.07, 0.07], 0.9290	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	2/24 (8.3)	5/46 (10.9)	3/26 (11.5)	13/102 (12.7)	5/50 (10.0)
RR [95%-CI]; p-value	1.71 [0.39, 7.48], 0.4735		0.94 [0.24, 3.63], 0.9308		1.27 [0.48, 3.38], 0.6256	
OR [95%-CI]; p-value	1.83 [0.36, 9.35], 0.4607		0.93 [0.20, 4.27], 0.9309		1.31 [0.44, 3.92], 0.6226	
RD [95%-CI]; p-value	0.06 [-0.08, 0.20], 0.4166		-0.01 [-0.16, 0.15], 0.9314		0.03 [-0.08, 0.13], 0.6096	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7825		0.3848		0.7231	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	5/48 (10.4)	6/98 (6.1)	3/46 (6.5)	12/183 (6.6)	8/94 (8.5)
RR [95%-CI]; p-value	0.68 [0.22, 2.10], 0.5008		0.94 [0.25, 3.59], 0.9264		0.77 [0.33, 1.82], 0.5521	
OR [95%-CI]; p-value	0.65 [0.19, 2.27], 0.4995		0.93 [0.22, 3.92], 0.9265		0.75 [0.30, 1.91], 0.5520	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5194		-0.00 [-0.09, 0.08], 0.9272		-0.02 [-0.09, 0.05], 0.5668	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	4/24 (16.7)	5/46 (10.9)	1/26 (3.8)	10/102 (9.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.54 [0.16, 1.82], 0.3179		2.83 [0.35, 22.91], 0.3305		0.98 [0.35, 2.72], 0.9696	
OR [95%-CI]; p-value	0.49 [0.12, 2.01], 0.3155		3.05 [0.34, 27.62], 0.3003		0.98 [0.32, 3.03], 0.9696	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.09], 0.3631		0.07 [-0.05, 0.19], 0.2371		-0.00 [-0.10, 0.10], 0.9697	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.4542		0.0537		0.1169	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	19/85 (22.4)	13/48 (27.1)	19/98 (19.4)	2/46 (4.3)	38/183 (20.8)	15/94 (16.0)
RR [95%-CI]; p-value	0.83 [0.45, 1.52], 0.5376		4.46 [1.08, 18.34], 0.0383		1.30 [0.76, 2.24], 0.3422	
OR [95%-CI]; p-value	0.78 [0.34, 1.75], 0.5399		5.29 [1.18, 23.78], 0.0171		1.38 [0.72, 2.66], 0.3355	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.11], 0.5466		0.15 [0.05, 0.25], 0.0026		0.05 [-0.05, 0.14], 0.3188	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	9/56 (16.1)	7/24 (29.2)	7/46 (15.2)	5/26 (19.2)	16/102 (15.7)	12/50 (24.0)
RR [95%-CI]; p-value	0.55 [0.23, 1.31], 0.1765		0.79 [0.28, 2.24], 0.6597		0.65 [0.34, 1.27], 0.2119	
OR [95%-CI]; p-value	0.47 [0.15, 1.44], 0.1796		0.75 [0.21, 2.67], 0.6607		0.59 [0.25, 1.36], 0.2141	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.07], 0.2122		-0.04 [-0.22, 0.14], 0.6684		-0.08 [-0.22, 0.05], 0.2371	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.8535		0.8521		0.9699	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	12/85 (14.1)	10/48 (20.8)	11/98 (11.2)	7/46 (15.2)	23/183 (12.6)	17/94 (18.1)
RR [95%-CI]; p-value	0.68 [0.32, 1.45], 0.3162		0.74 [0.31, 1.78], 0.4981		0.69 [0.39, 1.24], 0.2152	
OR [95%-CI]; p-value	0.62 [0.25, 1.58], 0.3168		0.70 [0.25, 1.95], 0.4993		0.65 [0.33, 1.29], 0.2161	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3355		-0.04 [-0.16, 0.08], 0.5183		-0.06 [-0.15, 0.04], 0.2370	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	7/56 (12.5)	5/24 (20.8)	6/46 (13.0)	4/26 (15.4)	13/102 (12.7)	9/50 (18.0)
RR [95%-CI]; p-value	0.60 [0.21, 1.70], 0.3372		0.85 [0.26, 2.73], 0.7822		0.71 [0.32, 1.54], 0.3855	
OR [95%-CI]; p-value	0.54 [0.15, 1.92], 0.3388		0.83 [0.21, 3.24], 0.7826		0.67 [0.26, 1.68], 0.3870	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.10], 0.3750		-0.02 [-0.19, 0.15], 0.7865		-0.05 [-0.18, 0.07], 0.4085	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9492		0.1352		0.3619	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	24/85 (28.2)	14/48 (29.2)	26/98 (26.5)	9/46 (19.6)	50/183 (27.3)	23/94 (24.5)
RR [95%-CI]; p-value	0.97 [0.56, 1.69], 0.9089		1.36 [0.69, 2.66], 0.3746		1.12 [0.73, 1.71], 0.6122	
OR [95%-CI]; p-value	0.96 [0.44, 2.09], 0.9091		1.48 [0.63, 3.49], 0.3636		1.16 [0.66, 2.06], 0.6097	
RD [95%-CI]; p-value	-0.01 [-0.17, 0.15], 0.9093		0.07 [-0.07, 0.21], 0.3436		0.03 [-0.08, 0.14], 0.6053	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	14/56 (25.0)	6/24 (25.0)	7/46 (15.2)	7/26 (26.9)	21/102 (20.6)	13/50 (26.0)
RR [95%-CI]; p-value	1.00 [0.44, 2.29], 1.0000		0.57 [0.22, 1.43], 0.2296		0.79 [0.43, 1.45], 0.4483	
OR [95%-CI]; p-value	1.00 [0.33, 3.02], 1.0000		0.49 [0.15, 1.59], 0.2280		0.74 [0.33, 1.63], 0.4519	
RD [95%-CI]; p-value	0.00 [-0.21, 0.21], 1.0000		-0.12 [-0.32, 0.08], 0.2504		-0.05 [-0.20, 0.09], 0.4636	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.7309		0.9405		0.7863	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	14/85 (16.5)	4/48 (8.3)	8/98 (8.2)	2/46 (4.3)	22/183 (12.0)	6/94 (6.4)
RR [95%-CI]; p-value	1.98 [0.69, 5.67], 0.2049		1.88 [0.42, 8.49], 0.4133		1.88 [0.79, 4.49], 0.1527	
OR [95%-CI]; p-value	2.17 [0.67, 7.01], 0.1877		1.96 [0.40, 9.60], 0.4010		2.00 [0.78, 5.13], 0.1404	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1509		0.04 [-0.04, 0.12], 0.3503		0.06 [-0.01, 0.12], 0.1055	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	3/56 (5.4)	1/24 (4.2)	3/46 (6.5)	1/26 (3.8)	6/102 (5.9)	2/50 (4.0)
RR [95%-CI]; p-value	1.29 [0.14, 11.74], 0.8238		1.70 [0.19, 15.48], 0.6398		1.47 [0.31, 7.03], 0.6289	
OR [95%-CI]; p-value	1.30 [0.13, 13.19], 0.8228		1.74 [0.17, 17.68], 0.6340		1.50 [0.29, 7.71], 0.6253	
RD [95%-CI]; p-value	0.01 [-0.09, 0.11], 0.8143		0.03 [-0.08, 0.13], 0.6098		0.02 [-0.05, 0.09], 0.6031	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.9874		0.2437		0.3967	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	9/85 (10.6)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	16/183 (8.7)	11/94 (11.7)
RR [95%-CI]; p-value	0.85 [0.32, 2.24], 0.7375		0.66 [0.22, 1.96], 0.4515		0.75 [0.36, 1.54], 0.4315	
OR [95%-CI]; p-value	0.83 [0.28, 2.49], 0.7378		0.63 [0.19, 2.11], 0.4506		0.72 [0.32, 1.63], 0.4318	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.10], 0.7427		-0.04 [-0.14, 0.07], 0.4799		-0.03 [-0.11, 0.05], 0.4501	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	2/26 (7.7)	15/102 (14.7)	6/50 (12.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		1.98 [0.44, 8.83], 0.3715		1.23 [0.51, 2.97], 0.6522	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		2.15 [0.41, 11.23], 0.3537		1.26 [0.46, 3.48], 0.6497	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		0.08 [-0.07, 0.22], 0.3118		0.03 [-0.09, 0.14], 0.6397	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.9724		0.9391		0.9504	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	17/85 (20.0)	14/48 (29.2)	18/98 (18.4)	9/46 (19.6)	35/183 (19.1)	23/94 (24.5)
RR [95%-CI]; p-value	0.69 [0.37, 1.27], 0.2273		0.94 [0.46, 1.93], 0.8633		0.78 [0.49, 1.24], 0.2977	
OR [95%-CI]; p-value	0.61 [0.27, 1.38], 0.2298		0.93 [0.38, 2.25], 0.8637		0.73 [0.40, 1.33], 0.3008	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.06], 0.2438		-0.01 [-0.15, 0.13], 0.8648		-0.05 [-0.16, 0.05], 0.3137	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	11/56 (19.6)	7/24 (29.2)	7/46 (15.2)	4/26 (15.4)	18/102 (17.6)	11/50 (22.0)
RR [95%-CI]; p-value	0.67 [0.30, 1.53], 0.3436		0.99 [0.32, 3.06], 0.9849		0.80 [0.41, 1.57], 0.5186	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3499		0.99 [0.26, 3.75], 0.9849		0.76 [0.33, 1.76], 0.5211	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3730		-0.00 [-0.17, 0.17], 0.9849		-0.04 [-0.18, 0.09], 0.5322	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0894		0.8651		0.2899	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	16/85 (18.8)	12/48 (25.0)	13/98 (13.3)	8/46 (17.4)	29/183 (15.8)	20/94 (21.3)
RR [95%-CI]; p-value	0.75 [0.39, 1.46], 0.3991		0.76 [0.34, 1.71], 0.5113		0.74 [0.45, 1.24], 0.2599	
OR [95%-CI]; p-value	0.70 [0.30, 1.63], 0.4014		0.73 [0.28, 1.90], 0.5131		0.70 [0.37, 1.31], 0.2621	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4135		-0.04 [-0.17, 0.09], 0.5291		-0.05 [-0.15, 0.04], 0.2785	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	11/24 (45.8)	9/46 (19.6)	6/26 (23.1)	17/102 (16.7)	17/50 (34.0)
RR [95%-CI]; p-value	0.31 [0.14, 0.68], 0.0032		0.85 [0.34, 2.12], 0.7234		0.49 [0.27, 0.88], 0.0162	
OR [95%-CI]; p-value	0.20 [0.07, 0.59], 0.0024		0.81 [0.25, 2.61], 0.7245		0.39 [0.18, 0.85], 0.0160	
RD [95%-CI]; p-value	-0.32 [-0.53, -0.10], 0.0048		-0.04 [-0.23, 0.16], 0.7287		-0.17 [-0.32, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.0554		0.7179		0.1198	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	4/85 (4.7)	10/48 (20.8)	12/98 (12.2)	5/46 (10.9)	16/183 (8.7)	15/94 (16.0)
RR [95%-CI]; p-value	0.23 [0.07, 0.68], 0.0083		1.13 [0.42, 3.01], 0.8122		0.55 [0.28, 1.06], 0.0736	
OR [95%-CI]; p-value	0.19 [0.06, 0.64], 0.0036		1.14 [0.38, 3.46], 0.8115		0.50 [0.24, 1.07], 0.0713	
RD [95%-CI]; p-value	-0.16 [-0.28, -0.04], 0.0104		0.01 [-0.10, 0.12], 0.8080		-0.07 [-0.16, 0.01], 0.0946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	3/24 (12.5)	8/46 (17.4)	3/26 (11.5)	16/102 (15.7)	6/50 (12.0)
RR [95%-CI]; p-value	1.14 [0.33, 3.94], 0.8325		1.51 [0.44, 5.19], 0.5155		1.31 [0.54, 3.14], 0.5485	
OR [95%-CI]; p-value	1.17 [0.28, 4.84], 0.8317		1.61 [0.39, 6.71], 0.5073		1.36 [0.50, 3.73], 0.5439	
RD [95%-CI]; p-value	0.02 [-0.14, 0.18], 0.8279		0.06 [-0.11, 0.22], 0.4857		0.04 [-0.08, 0.15], 0.5278	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7853		0.5925		0.9762	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	8/48 (16.7)	10/98 (10.2)	3/46 (6.5)	20/183 (10.9)	11/94 (11.7)
RR [95%-CI]; p-value	0.71 [0.30, 1.67], 0.4272		1.56 [0.45, 5.42], 0.4798		0.93 [0.47, 1.87], 0.8466	
OR [95%-CI]; p-value	0.67 [0.24, 1.82], 0.4274		1.63 [0.43, 6.23], 0.4722		0.93 [0.42, 2.02], 0.8468	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.08], 0.4448		0.04 [-0.06, 0.13], 0.4386		-0.01 [-0.09, 0.07], 0.8482	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	4/26 (15.4)	15/102 (14.7)	8/50 (16.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		0.99 [0.32, 3.06], 0.9849		0.92 [0.42, 2.02], 0.8340	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		0.99 [0.26, 3.75], 0.9849		0.91 [0.36, 2.30], 0.8343	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		-0.00 [-0.17, 0.17], 0.9849		-0.01 [-0.14, 0.11], 0.8362	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4512		0.8494		0.5091	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	10/98 (10.2)	4/46 (8.7)	15/183 (8.2)	11/94 (11.7)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.17 [0.39, 3.54], 0.7767		0.70 [0.34, 1.46], 0.3439	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.19 [0.35, 4.03], 0.7757		0.67 [0.30, 1.53], 0.3435	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.02 [-0.09, 0.12], 0.7700		-0.04 [-0.11, 0.04], 0.3671	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	2/24 (8.3)	5/46 (10.9)	2/26 (7.7)	9/102 (8.8)	4/50 (8.0)
RR [95%-CI]; p-value	0.86 [0.17, 4.37], 0.8528		1.41 [0.29, 6.78], 0.6656		1.10 [0.36, 3.41], 0.8648	
OR [95%-CI]; p-value	0.85 [0.14, 4.96], 0.8530		1.46 [0.26, 8.14], 0.6620		1.11 [0.33, 3.81], 0.8646	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8570		0.03 [-0.10, 0.17], 0.6478		0.01 [-0.08, 0.10], 0.8625	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7430		0.5876		0.8696	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	17/183 (9.3)	11/94 (11.7)
RR [95%-CI]; p-value	0.94 [0.36, 2.43], 0.9003		0.66 [0.22, 1.96], 0.4515		0.79 [0.39, 1.63], 0.5277	
OR [95%-CI]; p-value	0.93 [0.32, 2.75], 0.9004		0.63 [0.19, 2.11], 0.4506		0.77 [0.35, 1.72], 0.5282	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.11], 0.9011		-0.04 [-0.14, 0.07], 0.4799		-0.02 [-0.10, 0.05], 0.5413	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	3/24 (12.5)	4/46 (8.7)	2/26 (7.7)	9/102 (8.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.71 [0.19, 2.75], 0.6250		1.13 [0.22, 5.76], 0.8826		0.88 [0.31, 2.50], 0.8134	
OR [95%-CI]; p-value	0.69 [0.15, 3.13], 0.6256		1.14 [0.19, 6.71], 0.8824		0.87 [0.28, 2.75], 0.8137	
RD [95%-CI]; p-value	-0.04 [-0.19, 0.12], 0.6450		0.01 [-0.12, 0.14], 0.8805		-0.01 [-0.11, 0.09], 0.8171	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.3.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5278		0.5312		0.5768	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	9/48 (18.8)	5/98 (5.1)	0/46 (0.0)	10/183 (5.5)	9/94 (9.6)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		4.74 [0.26, 85.04], 0.2903		0.57 [0.24, 1.36], 0.2041	
OR [95%-CI]; p-value	0.27 [0.09, 0.86], 0.0202		4.95 [0.26, 92.49], 0.2373		0.55 [0.21, 1.39], 0.2001	
RD [95%-CI]; p-value	-0.13 [-0.25, -0.01], 0.0375		0.04 [-0.01, 0.09], 0.1342		-0.04 [-0.11, 0.03], 0.2361	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	3/24 (12.5)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	3/50 (6.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.30], 0.0847		1.15 [0.04, 33.20], 0.9342		0.33 [0.06, 1.89], 0.2121	
OR [95%-CI]; p-value	0.13 [0.01, 1.29], 0.0439		1.16 [0.04, 35.64], 0.9341		0.31 [0.05, 1.94], 0.1896	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1247		0.00 [-0.06, 0.07], 0.9328		-0.04 [-0.11, 0.03], 0.2656	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_3_m_pt_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.3.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.7405		0.3473		0.2783	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	7/98 (7.1)	2/46 (4.3)	12/183 (6.6)	9/94 (9.6)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.64 [0.36, 7.60], 0.5253		0.68 [0.30, 1.57], 0.3701	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.69 [0.34, 8.48], 0.5182		0.66 [0.27, 1.63], 0.3691	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.03 [-0.05, 0.11], 0.4821		-0.03 [-0.10, 0.04], 0.3946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	3/24 (12.5)	0/46 (0.0)	1/26 (3.8)	2/102 (2.0)	4/50 (8.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.60], 0.1544		0.28 [0.01, 8.05], 0.4573		0.25 [0.05, 1.29], 0.0975	
OR [95%-CI]; p-value	0.26 [0.04, 1.66], 0.1306		0.27 [0.01, 8.39], 0.4267		0.23 [0.04, 1.30], 0.0724	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2144		-0.03 [-0.11, 0.05], 0.4953		-0.06 [-0.14, 0.02], 0.1383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_3_m_pt_ae10pct_race.sas using SAS 9.4

Table 12.4.8.1.1.s4
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.7974		0.7556		0.7759	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	3/48 (6.3)	4/98 (4.1)	2/46 (4.3)	10/183 (5.5)	5/94 (5.3)
RR [95%-CI]; p-value	1.13 [0.30, 4.31], 0.8587		0.94 [0.18, 4.94], 0.9406		1.03 [0.36, 2.92], 0.9597	
OR [95%-CI]; p-value	1.14 [0.27, 4.78], 0.8584		0.94 [0.17, 5.31], 0.9406		1.03 [0.34, 3.10], 0.9596	
RD [95%-CI]; p-value	0.01 [-0.08, 0.10], 0.8562		-0.00 [-0.07, 0.07], 0.9412		0.00 [-0.05, 0.06], 0.9595	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	0/24 (0.0)	1/46 (2.2)	1/26 (3.8)	3/102 (2.9)	1/50 (2.0)
RR [95%-CI]; p-value	1.75 [0.08, 37.41], 0.7202		0.57 [0.04, 8.66], 0.6821		1.47 [0.16, 13.78], 0.7355	
OR [95%-CI]; p-value	1.78 [0.08, 40.91], 0.7157		0.56 [0.03, 9.27], 0.6783		1.48 [0.15, 14.65], 0.7334	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6858		-0.02 [-0.10, 0.07], 0.7001		0.01 [-0.04, 0.06], 0.7165	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_8_1_1_m_soc_sae5pct_race.sas using SAS 9.4

Table 12.4.8.1.2.s4
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_8_1_2_m_pt_sae5pct_race.sas using SAS 9.4

Table 12.4.5.1.1.s4
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_5_1_1_m_soc_aeg35pct_race.sas using SAS 9.4

Table 12.4.5.1.2.s4
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_5_1_2_m_pt_aeg35pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7825		0.3848		0.7231	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	5/48 (10.4)	6/98 (6.1)	3/46 (6.5)	12/183 (6.6)	8/94 (8.5)
RR [95%-CI]; p-value	0.68 [0.22, 2.10], 0.5008		0.94 [0.25, 3.59], 0.9264		0.77 [0.33, 1.82], 0.5521	
OR [95%-CI]; p-value	0.65 [0.19, 2.27], 0.4995		0.93 [0.22, 3.92], 0.9265		0.75 [0.30, 1.91], 0.5520	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5194		-0.00 [-0.09, 0.08], 0.9272		-0.02 [-0.09, 0.05], 0.5668	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	4/24 (16.7)	5/46 (10.9)	1/26 (3.8)	10/102 (9.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.54 [0.16, 1.82], 0.3179		2.83 [0.35, 22.91], 0.3305		0.98 [0.35, 2.72], 0.9696	
OR [95%-CI]; p-value	0.49 [0.12, 2.01], 0.3155		3.05 [0.34, 27.62], 0.3003		0.98 [0.32, 3.03], 0.9696	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.09], 0.3631		0.07 [-0.05, 0.19], 0.2371		-0.00 [-0.10, 0.10], 0.9697	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.4542		0.0537		0.1169	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	19/85 (22.4)	13/48 (27.1)	19/98 (19.4)	2/46 (4.3)	38/183 (20.8)	15/94 (16.0)
RR [95%-CI]; p-value	0.83 [0.45, 1.52], 0.5376		4.46 [1.08, 18.34], 0.0383		1.30 [0.76, 2.24], 0.3422	
OR [95%-CI]; p-value	0.78 [0.34, 1.75], 0.5399		5.29 [1.18, 23.78], 0.0171		1.38 [0.72, 2.66], 0.3355	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.11], 0.5466		0.15 [0.05, 0.25], 0.0026		0.05 [-0.05, 0.14], 0.3188	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	9/56 (16.1)	7/24 (29.2)	7/46 (15.2)	5/26 (19.2)	16/102 (15.7)	12/50 (24.0)
RR [95%-CI]; p-value	0.55 [0.23, 1.31], 0.1765		0.79 [0.28, 2.24], 0.6597		0.65 [0.34, 1.27], 0.2119	
OR [95%-CI]; p-value	0.47 [0.15, 1.44], 0.1796		0.75 [0.21, 2.67], 0.6607		0.59 [0.25, 1.36], 0.2141	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.07], 0.2122		-0.04 [-0.22, 0.14], 0.6684		-0.08 [-0.22, 0.05], 0.2371	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.8535		0.8521		0.9699	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	12/85 (14.1)	10/48 (20.8)	11/98 (11.2)	7/46 (15.2)	23/183 (12.6)	17/94 (18.1)
RR [95%-CI]; p-value	0.68 [0.32, 1.45], 0.3162		0.74 [0.31, 1.78], 0.4981		0.69 [0.39, 1.24], 0.2152	
OR [95%-CI]; p-value	0.62 [0.25, 1.58], 0.3168		0.70 [0.25, 1.95], 0.4993		0.65 [0.33, 1.29], 0.2161	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3355		-0.04 [-0.16, 0.08], 0.5183		-0.06 [-0.15, 0.04], 0.2370	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	7/56 (12.5)	5/24 (20.8)	6/46 (13.0)	4/26 (15.4)	13/102 (12.7)	9/50 (18.0)
RR [95%-CI]; p-value	0.60 [0.21, 1.70], 0.3372		0.85 [0.26, 2.73], 0.7822		0.71 [0.32, 1.54], 0.3855	
OR [95%-CI]; p-value	0.54 [0.15, 1.92], 0.3388		0.83 [0.21, 3.24], 0.7826		0.67 [0.26, 1.68], 0.3870	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.10], 0.3750		-0.02 [-0.19, 0.15], 0.7865		-0.05 [-0.18, 0.07], 0.4085	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9492		0.1352		0.3619	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	24/85 (28.2)	14/48 (29.2)	26/98 (26.5)	9/46 (19.6)	50/183 (27.3)	23/94 (24.5)
RR [95%-CI]; p-value	0.97 [0.56, 1.69], 0.9089		1.36 [0.69, 2.66], 0.3746		1.12 [0.73, 1.71], 0.6122	
OR [95%-CI]; p-value	0.96 [0.44, 2.09], 0.9091		1.48 [0.63, 3.49], 0.3636		1.16 [0.66, 2.06], 0.6097	
RD [95%-CI]; p-value	-0.01 [-0.17, 0.15], 0.9093		0.07 [-0.07, 0.21], 0.3436		0.03 [-0.08, 0.14], 0.6053	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	14/56 (25.0)	6/24 (25.0)	7/46 (15.2)	7/26 (26.9)	21/102 (20.6)	13/50 (26.0)
RR [95%-CI]; p-value	1.00 [0.44, 2.29], 1.0000		0.57 [0.22, 1.43], 0.2296		0.79 [0.43, 1.45], 0.4483	
OR [95%-CI]; p-value	1.00 [0.33, 3.02], 1.0000		0.49 [0.15, 1.59], 0.2280		0.74 [0.33, 1.63], 0.4519	
RD [95%-CI]; p-value	0.00 [-0.21, 0.21], 1.0000		-0.12 [-0.32, 0.08], 0.2504		-0.05 [-0.20, 0.09], 0.4636	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.7309		0.9405		0.7863	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	14/85 (16.5)	4/48 (8.3)	8/98 (8.2)	2/46 (4.3)	22/183 (12.0)	6/94 (6.4)
RR [95%-CI]; p-value	1.98 [0.69, 5.67], 0.2049		1.88 [0.42, 8.49], 0.4133		1.88 [0.79, 4.49], 0.1527	
OR [95%-CI]; p-value	2.17 [0.67, 7.01], 0.1877		1.96 [0.40, 9.60], 0.4010		2.00 [0.78, 5.13], 0.1404	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1509		0.04 [-0.04, 0.12], 0.3503		0.06 [-0.01, 0.12], 0.1055	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	3/56 (5.4)	1/24 (4.2)	3/46 (6.5)	1/26 (3.8)	6/102 (5.9)	2/50 (4.0)
RR [95%-CI]; p-value	1.29 [0.14, 11.74], 0.8238		1.70 [0.19, 15.48], 0.6398		1.47 [0.31, 7.03], 0.6289	
OR [95%-CI]; p-value	1.30 [0.13, 13.19], 0.8228		1.74 [0.17, 17.68], 0.6340		1.50 [0.29, 7.71], 0.6253	
RD [95%-CI]; p-value	0.01 [-0.09, 0.11], 0.8143		0.03 [-0.08, 0.13], 0.6098		0.02 [-0.05, 0.09], 0.6031	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.9874		0.2437		0.3967	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	9/85 (10.6)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	16/183 (8.7)	11/94 (11.7)
RR [95%-CI]; p-value	0.85 [0.32, 2.24], 0.7375		0.66 [0.22, 1.96], 0.4515		0.75 [0.36, 1.54], 0.4315	
OR [95%-CI]; p-value	0.83 [0.28, 2.49], 0.7378		0.63 [0.19, 2.11], 0.4506		0.72 [0.32, 1.63], 0.4318	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.10], 0.7427		-0.04 [-0.14, 0.07], 0.4799		-0.03 [-0.11, 0.05], 0.4501	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	2/26 (7.7)	15/102 (14.7)	6/50 (12.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		1.98 [0.44, 8.83], 0.3715		1.23 [0.51, 2.97], 0.6522	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		2.15 [0.41, 11.23], 0.3537		1.26 [0.46, 3.48], 0.6497	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		0.08 [-0.07, 0.22], 0.3118		0.03 [-0.09, 0.14], 0.6397	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.9724		0.9391		0.9504	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	17/85 (20.0)	14/48 (29.2)	18/98 (18.4)	9/46 (19.6)	35/183 (19.1)	23/94 (24.5)
RR [95%-CI]; p-value	0.69 [0.37, 1.27], 0.2273		0.94 [0.46, 1.93], 0.8633		0.78 [0.49, 1.24], 0.2977	
OR [95%-CI]; p-value	0.61 [0.27, 1.38], 0.2298		0.93 [0.38, 2.25], 0.8637		0.73 [0.40, 1.33], 0.3008	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.06], 0.2438		-0.01 [-0.15, 0.13], 0.8648		-0.05 [-0.16, 0.05], 0.3137	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	11/56 (19.6)	7/24 (29.2)	7/46 (15.2)	4/26 (15.4)	18/102 (17.6)	11/50 (22.0)
RR [95%-CI]; p-value	0.67 [0.30, 1.53], 0.3436		0.99 [0.32, 3.06], 0.9849		0.80 [0.41, 1.57], 0.5186	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3499		0.99 [0.26, 3.75], 0.9849		0.76 [0.33, 1.76], 0.5211	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3730		-0.00 [-0.17, 0.17], 0.9849		-0.04 [-0.18, 0.09], 0.5322	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0894		0.8651		0.2899	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	16/85 (18.8)	12/48 (25.0)	13/98 (13.3)	8/46 (17.4)	29/183 (15.8)	20/94 (21.3)
RR [95%-CI]; p-value	0.75 [0.39, 1.46], 0.3991		0.76 [0.34, 1.71], 0.5113		0.74 [0.45, 1.24], 0.2599	
OR [95%-CI]; p-value	0.70 [0.30, 1.63], 0.4014		0.73 [0.28, 1.90], 0.5131		0.70 [0.37, 1.31], 0.2621	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4135		-0.04 [-0.17, 0.09], 0.5291		-0.05 [-0.15, 0.04], 0.2785	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	11/24 (45.8)	9/46 (19.6)	6/26 (23.1)	17/102 (16.7)	17/50 (34.0)
RR [95%-CI]; p-value	0.31 [0.14, 0.68], 0.0032		0.85 [0.34, 2.12], 0.7234		0.49 [0.27, 0.88], 0.0162	
OR [95%-CI]; p-value	0.20 [0.07, 0.59], 0.0024		0.81 [0.25, 2.61], 0.7245		0.39 [0.18, 0.85], 0.0160	
RD [95%-CI]; p-value	-0.32 [-0.53, -0.10], 0.0048		-0.04 [-0.23, 0.16], 0.7287		-0.17 [-0.32, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.0554		0.7179		0.1198	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	4/85 (4.7)	10/48 (20.8)	12/98 (12.2)	5/46 (10.9)	16/183 (8.7)	15/94 (16.0)
RR [95%-CI]; p-value	0.23 [0.07, 0.68], 0.0083		1.13 [0.42, 3.01], 0.8122		0.55 [0.28, 1.06], 0.0736	
OR [95%-CI]; p-value	0.19 [0.06, 0.64], 0.0036		1.14 [0.38, 3.46], 0.8115		0.50 [0.24, 1.07], 0.0713	
RD [95%-CI]; p-value	-0.16 [-0.28, -0.04], 0.0104		0.01 [-0.10, 0.12], 0.8080		-0.07 [-0.16, 0.01], 0.0946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	3/24 (12.5)	8/46 (17.4)	3/26 (11.5)	16/102 (15.7)	6/50 (12.0)
RR [95%-CI]; p-value	1.14 [0.33, 3.94], 0.8325		1.51 [0.44, 5.19], 0.5155		1.31 [0.54, 3.14], 0.5485	
OR [95%-CI]; p-value	1.17 [0.28, 4.84], 0.8317		1.61 [0.39, 6.71], 0.5073		1.36 [0.50, 3.73], 0.5439	
RD [95%-CI]; p-value	0.02 [-0.14, 0.18], 0.8279		0.06 [-0.11, 0.22], 0.4857		0.04 [-0.08, 0.15], 0.5278	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.2439		0.8808		0.4760	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	7/85 (8.2)	2/48 (4.2)	7/98 (7.1)	4/46 (8.7)	14/183 (7.7)	6/94 (6.4)
RR [95%-CI]; p-value	1.98 [0.43, 9.14], 0.3831		0.82 [0.25, 2.67], 0.7433		1.20 [0.48, 3.02], 0.7007	
OR [95%-CI]; p-value	2.06 [0.41, 10.36], 0.3696		0.81 [0.22, 2.91], 0.7436		1.21 [0.45, 3.27], 0.6996	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3267		-0.02 [-0.11, 0.08], 0.7514		0.01 [-0.05, 0.08], 0.6918	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	3/24 (12.5)	5/46 (10.9)	3/26 (11.5)	9/102 (8.8)	6/50 (12.0)
RR [95%-CI]; p-value	0.57 [0.14, 2.36], 0.4394		0.94 [0.24, 3.63], 0.9308		0.74 [0.28, 1.95], 0.5369	
OR [95%-CI]; p-value	0.54 [0.11, 2.62], 0.4371		0.93 [0.20, 4.27], 0.9309		0.71 [0.24, 2.12], 0.5373	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.09], 0.4796		-0.01 [-0.16, 0.15], 0.9314		-0.03 [-0.14, 0.07], 0.5553	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7853		0.5925		0.9762	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	8/48 (16.7)	10/98 (10.2)	3/46 (6.5)	20/183 (10.9)	11/94 (11.7)
RR [95%-CI]; p-value	0.71 [0.30, 1.67], 0.4272		1.56 [0.45, 5.42], 0.4798		0.93 [0.47, 1.87], 0.8466	
OR [95%-CI]; p-value	0.67 [0.24, 1.82], 0.4274		1.63 [0.43, 6.23], 0.4722		0.93 [0.42, 2.02], 0.8468	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.08], 0.4448		0.04 [-0.06, 0.13], 0.4386		-0.01 [-0.09, 0.07], 0.8482	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	4/26 (15.4)	15/102 (14.7)	8/50 (16.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		0.99 [0.32, 3.06], 0.9849		0.92 [0.42, 2.02], 0.8340	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		0.99 [0.26, 3.75], 0.9849		0.91 [0.36, 2.30], 0.8343	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		-0.00 [-0.17, 0.17], 0.9849		-0.01 [-0.14, 0.11], 0.8362	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4512		0.8494		0.5091	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	10/98 (10.2)	4/46 (8.7)	15/183 (8.2)	11/94 (11.7)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.17 [0.39, 3.54], 0.7767		0.70 [0.34, 1.46], 0.3439	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.19 [0.35, 4.03], 0.7757		0.67 [0.30, 1.53], 0.3435	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.02 [-0.09, 0.12], 0.7700		-0.04 [-0.11, 0.04], 0.3671	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	2/24 (8.3)	5/46 (10.9)	2/26 (7.7)	9/102 (8.8)	4/50 (8.0)
RR [95%-CI]; p-value	0.86 [0.17, 4.37], 0.8528		1.41 [0.29, 6.78], 0.6656		1.10 [0.36, 3.41], 0.8648	
OR [95%-CI]; p-value	0.85 [0.14, 4.96], 0.8530		1.46 [0.26, 8.14], 0.6620		1.11 [0.33, 3.81], 0.8646	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8570		0.03 [-0.10, 0.17], 0.6478		0.01 [-0.08, 0.10], 0.8625	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7430		0.5876		0.8696	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	17/183 (9.3)	11/94 (11.7)
RR [95%-CI]; p-value	0.94 [0.36, 2.43], 0.9003		0.66 [0.22, 1.96], 0.4515		0.79 [0.39, 1.63], 0.5277	
OR [95%-CI]; p-value	0.93 [0.32, 2.75], 0.9004		0.63 [0.19, 2.11], 0.4506		0.77 [0.35, 1.72], 0.5282	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.11], 0.9011		-0.04 [-0.14, 0.07], 0.4799		-0.02 [-0.10, 0.05], 0.5413	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	3/24 (12.5)	4/46 (8.7)	2/26 (7.7)	9/102 (8.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.71 [0.19, 2.75], 0.6250		1.13 [0.22, 5.76], 0.8826		0.88 [0.31, 2.50], 0.8134	
OR [95%-CI]; p-value	0.69 [0.15, 3.13], 0.6256		1.14 [0.19, 6.71], 0.8824		0.87 [0.28, 2.75], 0.8137	
RD [95%-CI]; p-value	-0.04 [-0.19, 0.12], 0.6450		0.01 [-0.12, 0.14], 0.8805		-0.01 [-0.11, 0.09], 0.8171	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.4.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5278		0.5312		0.5768	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	9/48 (18.8)	5/98 (5.1)	0/46 (0.0)	10/183 (5.5)	9/94 (9.6)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		4.74 [0.26, 85.04], 0.2903		0.57 [0.24, 1.36], 0.2041	
OR [95%-CI]; p-value	0.27 [0.09, 0.86], 0.0202		4.95 [0.26, 92.49], 0.2373		0.55 [0.21, 1.39], 0.2001	
RD [95%-CI]; p-value	-0.13 [-0.25, -0.01], 0.0375		0.04 [-0.01, 0.09], 0.1342		-0.04 [-0.11, 0.03], 0.2361	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	3/24 (12.5)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	3/50 (6.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.30], 0.0847		1.15 [0.04, 33.20], 0.9342		0.33 [0.06, 1.89], 0.2121	
OR [95%-CI]; p-value	0.13 [0.01, 1.29], 0.0439		1.16 [0.04, 35.64], 0.9341		0.31 [0.05, 1.94], 0.1896	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1247		0.00 [-0.06, 0.07], 0.9328		-0.04 [-0.11, 0.03], 0.2656	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_4_m_pt_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.4.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.7405		0.3473		0.2783	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	7/98 (7.1)	2/46 (4.3)	12/183 (6.6)	9/94 (9.6)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.64 [0.36, 7.60], 0.5253		0.68 [0.30, 1.57], 0.3701	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.69 [0.34, 8.48], 0.5182		0.66 [0.27, 1.63], 0.3691	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.03 [-0.05, 0.11], 0.4821		-0.03 [-0.10, 0.04], 0.3946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	3/24 (12.5)	0/46 (0.0)	1/26 (3.8)	2/102 (2.0)	4/50 (8.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.60], 0.1544		0.28 [0.01, 8.05], 0.4573		0.25 [0.05, 1.29], 0.0975	
OR [95%-CI]; p-value	0.26 [0.04, 1.66], 0.1306		0.27 [0.01, 8.39], 0.4267		0.23 [0.04, 1.30], 0.0724	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2144		-0.03 [-0.11, 0.05], 0.4953		-0.06 [-0.14, 0.02], 0.1383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_4_m_pt_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.4.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.9034		0.7359		0.7017	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	3/48 (6.3)	5/98 (5.1)	4/46 (8.7)	10/183 (5.5)	7/94 (7.4)
RR [95%-CI]; p-value	0.94 [0.24, 3.77], 0.9317		0.59 [0.17, 2.08], 0.4096		0.73 [0.29, 1.87], 0.5157	
OR [95%-CI]; p-value	0.94 [0.21, 4.11], 0.9318		0.56 [0.14, 2.21], 0.4062		0.72 [0.26, 1.95], 0.5151	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.08], 0.9323		-0.04 [-0.13, 0.06], 0.4456		-0.02 [-0.08, 0.04], 0.5339	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	2/24 (8.3)	3/46 (6.5)	2/26 (7.7)	8/102 (7.8)	4/50 (8.0)
RR [95%-CI]; p-value	1.07 [0.22, 5.14], 0.9313		0.85 [0.15, 4.75], 0.8511		0.98 [0.31, 3.10], 0.9731	
OR [95%-CI]; p-value	1.08 [0.19, 5.99], 0.9312		0.84 [0.13, 5.37], 0.8511		0.98 [0.28, 3.42], 0.9731	
RD [95%-CI]; p-value	0.01 [-0.13, 0.14], 0.9303		-0.01 [-0.14, 0.11], 0.8542		-0.00 [-0.09, 0.09], 0.9732	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_4_m_pt_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.5143		0.1976		0.6952	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	1/48 (2.1)	4/98 (4.1)	5/46 (10.9)	14/183 (7.7)	6/94 (6.4)
RR [95%-CI]; p-value	5.65 [0.75, 42.78], 0.0938		0.38 [0.11, 1.33], 0.1298		1.20 [0.48, 3.02], 0.7007	
OR [95%-CI]; p-value	6.27 [0.78, 50.55], 0.0516		0.35 [0.09, 1.37], 0.1166		1.21 [0.45, 3.27], 0.6996	
RD [95%-CI]; p-value	0.10 [0.02, 0.18], 0.0170		-0.07 [-0.17, 0.03], 0.1751		0.01 [-0.05, 0.08], 0.6918	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	1/24 (4.2)	5/46 (10.9)	2/26 (7.7)	10/102 (9.8)	3/50 (6.0)
RR [95%-CI]; p-value	2.14 [0.26, 17.38], 0.4754		1.41 [0.29, 6.78], 0.6656		1.63 [0.47, 5.67], 0.4395	
OR [95%-CI]; p-value	2.25 [0.25, 20.41], 0.4587		1.46 [0.26, 8.14], 0.6620		1.70 [0.45, 6.49], 0.4308	
RD [95%-CI]; p-value	0.05 [-0.06, 0.16], 0.3936		0.03 [-0.10, 0.17], 0.6478		0.04 [-0.05, 0.13], 0.3944	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9130		0.5114		0.5226	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	1/183 (0.5)	1/94 (1.1)
RR [95%-CI]; p-value	1.14 [0.04, 33.40], 0.9389		0.23 [0.01, 6.84], 0.3985		0.51 [0.03, 8.12], 0.6362	
OR [95%-CI]; p-value	1.14 [0.04, 34.70], 0.9388		0.23 [0.01, 6.97], 0.3573		0.51 [0.03, 8.26], 0.6301	
RD [95%-CI]; p-value	0.00 [-0.04, 0.04], 0.9377		-0.02 [-0.06, 0.03], 0.4622		-0.01 [-0.03, 0.02], 0.6638	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
RR [95%-CI]; p-value	0.88 [0.03, 25.23], 0.9379		1.15 [0.04, 33.20], 0.9342		1.98 [0.09, 43.11], 0.6638	
OR [95%-CI]; p-value	0.87 [0.03, 26.91], 0.9379		1.16 [0.04, 35.64], 0.9341		2.00 [0.09, 45.18], 0.6568	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.06], 0.9395		0.00 [-0.06, 0.07], 0.9328		0.01 [-0.03, 0.05], 0.6197	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4706		0.4140		0.9794	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	9/85 (10.6)	1/48 (2.1)	4/98 (4.1)	4/46 (8.7)	13/183 (7.1)	5/94 (5.3)
RR [95%-CI]; p-value	5.08 [0.66, 38.91], 0.1175		0.47 [0.12, 1.79], 0.2689		1.34 [0.49, 3.63], 0.5710	
OR [95%-CI]; p-value	5.57 [0.68, 45.35], 0.0740		0.45 [0.11, 1.87], 0.2597		1.36 [0.47, 3.94], 0.5683	
RD [95%-CI]; p-value	0.09 [0.01, 0.16], 0.0301		-0.05 [-0.14, 0.04], 0.3169		0.02 [-0.04, 0.08], 0.5511	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	1/24 (4.2)	4/46 (8.7)	2/26 (7.7)	8/102 (7.8)	3/50 (6.0)
RR [95%-CI]; p-value	1.71 [0.20, 14.55], 0.6213		1.13 [0.22, 5.76], 0.8826		1.31 [0.36, 4.72], 0.6824	
OR [95%-CI]; p-value	1.77 [0.19, 16.71], 0.6143		1.14 [0.19, 6.71], 0.8824		1.33 [0.34, 5.26], 0.6803	
RD [95%-CI]; p-value	0.03 [-0.07, 0.13], 0.5771		0.01 [-0.12, 0.14], 0.8805		0.02 [-0.07, 0.10], 0.6671	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8012		0.7029		0.8913	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	1/48 (2.1)	1/98 (1.0)	0/46 (0.0)	6/183 (3.3)	1/94 (1.1)
RR [95%-CI]; p-value	2.82 [0.34, 23.47], 0.3367		0.95 [0.03, 27.78], 0.9758		3.08 [0.38, 25.23], 0.2940	
OR [95%-CI]; p-value	2.94 [0.33, 25.91], 0.3107		0.95 [0.03, 28.79], 0.9758		3.15 [0.37, 26.58], 0.2661	
RD [95%-CI]; p-value	0.04 [-0.03, 0.10], 0.2469		-0.00 [-0.04, 0.04], 0.9760		0.02 [-0.01, 0.06], 0.1897	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	0/24 (0.0)	2/46 (4.3)	0/26 (0.0)	4/102 (3.9)	0/50 (0.0)
RR [95%-CI]; p-value	1.75 [0.08, 37.41], 0.7202		2.30 [0.11, 49.24], 0.5931		3.96 [0.21, 73.48], 0.3556	
OR [95%-CI]; p-value	1.78 [0.08, 40.91], 0.7157		2.36 [0.10, 54.43], 0.5802		4.08 [0.21, 78.74], 0.3140	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6858		0.02 [-0.05, 0.10], 0.5387		0.03 [-0.02, 0.08], 0.2169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9495		0.4612		0.6563	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	5/48 (10.4)	7/98 (7.1)	4/46 (8.7)	13/183 (7.1)	9/94 (9.6)
RR [95%-CI]; p-value	0.68 [0.22, 2.10], 0.5008		0.82 [0.25, 2.67], 0.7433		0.74 [0.33, 1.67], 0.4716	
OR [95%-CI]; p-value	0.65 [0.19, 2.27], 0.4995		0.81 [0.22, 2.91], 0.7436		0.72 [0.30, 1.76], 0.4715	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5194		-0.02 [-0.11, 0.08], 0.7514		-0.02 [-0.09, 0.05], 0.4901	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	6/56 (10.7)	4/24 (16.7)	6/46 (13.0)	2/26 (7.7)	12/102 (11.8)	6/50 (12.0)
RR [95%-CI]; p-value	0.64 [0.20, 2.07], 0.4597		1.70 [0.37, 7.80], 0.4977		0.98 [0.39, 2.46], 0.9663	
OR [95%-CI]; p-value	0.60 [0.15, 2.35], 0.4607		1.80 [0.34, 9.64], 0.4877		0.98 [0.34, 2.78], 0.9664	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4917		0.05 [-0.09, 0.19], 0.4579		-0.00 [-0.11, 0.11], 0.9665	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9130		0.7932		0.6953	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	1/85 (1.2)	0/48 (0.0)	2/98 (2.0)	0/46 (0.0)	3/183 (1.6)	0/94 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.40], 0.9389		1.90 [0.09, 41.27], 0.6834		3.10 [0.16, 61.22], 0.4575	
OR [95%-CI]; p-value	1.14 [0.04, 34.70], 0.9388		1.92 [0.08, 43.36], 0.6775		3.13 [0.16, 63.20], 0.4322	
RD [95%-CI]; p-value	0.00 [-0.04, 0.04], 0.9377		0.01 [-0.03, 0.05], 0.6425		0.01 [-0.01, 0.03], 0.3545	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	0/24 (0.0)	2/46 (4.3)	1/26 (3.8)	3/102 (2.9)	1/50 (2.0)
RR [95%-CI]; p-value	0.88 [0.03, 25.23], 0.9379		1.13 [0.11, 11.87], 0.9186		1.47 [0.16, 13.78], 0.7355	
OR [95%-CI]; p-value	0.87 [0.03, 26.91], 0.9379		1.14 [0.10, 13.17], 0.9185		1.48 [0.15, 14.65], 0.7334	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.06], 0.9395		0.01 [-0.09, 0.10], 0.9172		0.01 [-0.04, 0.06], 0.7165	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.9517		0.6479		0.8104	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	5/48 (10.4)	6/98 (6.1)	4/46 (8.7)	11/183 (6.0)	9/94 (9.6)
RR [95%-CI]; p-value	0.56 [0.17, 1.85], 0.3458		0.70 [0.21, 2.37], 0.5716		0.63 [0.27, 1.46], 0.2803	
OR [95%-CI]; p-value	0.54 [0.15, 1.96], 0.3409		0.68 [0.18, 2.56], 0.5711		0.60 [0.24, 1.51], 0.2779	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3734		-0.03 [-0.12, 0.07], 0.5926		-0.04 [-0.10, 0.03], 0.3095	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	4/24 (16.7)	4/46 (8.7)	2/26 (7.7)	9/102 (8.8)	6/50 (12.0)
RR [95%-CI]; p-value	0.54 [0.16, 1.82], 0.3179		1.13 [0.22, 5.76], 0.8826		0.74 [0.28, 1.95], 0.5369	
OR [95%-CI]; p-value	0.49 [0.12, 2.01], 0.3155		1.14 [0.19, 6.71], 0.8824		0.71 [0.24, 2.12], 0.5373	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.09], 0.3631		0.01 [-0.12, 0.14], 0.8805		-0.03 [-0.14, 0.07], 0.5553	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.7580		0.6330		0.5308	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	3/85 (3.5)	0/48 (0.0)	3/98 (3.1)	0/46 (0.0)	6/183 (3.3)	0/94 (0.0)
RR [95%-CI]; p-value	3.42 [0.18, 66.93], 0.4172		2.85 [0.15, 55.69], 0.4904		6.20 [0.35, 109.76], 0.2136	
OR [95%-CI]; p-value	3.51 [0.17, 71.61], 0.3849		2.91 [0.14, 59.21], 0.4682		6.37 [0.35, 115.34], 0.1512	
RD [95%-CI]; p-value	0.02 [-0.02, 0.07], 0.3121		0.02 [-0.03, 0.07], 0.3890		0.03 [-0.00, 0.06], 0.0692	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	0/24 (0.0)	2/46 (4.3)	1/26 (3.8)	4/102 (3.9)	1/50 (2.0)
RR [95%-CI]; p-value	1.75 [0.08, 37.41], 0.7202		1.13 [0.11, 11.87], 0.9186		1.96 [0.22, 17.09], 0.5421	
OR [95%-CI]; p-value	1.78 [0.08, 40.91], 0.7157		1.14 [0.10, 13.17], 0.9185		2.00 [0.22, 18.38], 0.5326	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6858		0.01 [-0.09, 0.10], 0.9172		0.02 [-0.03, 0.07], 0.4862	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.6.s4
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.8718		0.1497		0.2622	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	15/85 (17.6)	12/48 (25.0)	23/98 (23.5)	5/46 (10.9)	38/183 (20.8)	17/94 (18.1)
RR [95%-CI]; p-value	0.71 [0.36, 1.38], 0.3094		2.16 [0.88, 5.32], 0.0942		1.15 [0.69, 1.92], 0.5990	
OR [95%-CI]; p-value	0.64 [0.27, 1.52], 0.3113		2.51 [0.89, 7.11], 0.0749		1.19 [0.63, 2.24], 0.5965	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.07], 0.3265		0.13 [0.00, 0.25], 0.0447		0.03 [-0.07, 0.12], 0.5901	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	9/56 (16.1)	6/24 (25.0)	5/46 (10.9)	4/26 (15.4)	14/102 (13.7)	10/50 (20.0)
RR [95%-CI]; p-value	0.64 [0.26, 1.61], 0.3443		0.71 [0.21, 2.40], 0.5779		0.69 [0.33, 1.43], 0.3171	
OR [95%-CI]; p-value	0.57 [0.18, 1.85], 0.3484		0.67 [0.16, 2.76], 0.5779		0.64 [0.26, 1.55], 0.3189	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.11], 0.3772		-0.05 [-0.21, 0.12], 0.5924		-0.06 [-0.19, 0.07], 0.3420	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_6_m_pt_adr_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE leading to death						
1.White n/N1 (%)	2/85 (2.4)	1/48 (2.1)	2/98 (2.0)	1/46 (2.2)	4/183 (2.2)	2/94 (2.1)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
Number of Patients with AE leading to treatment discontinuation						
1.White n/N1 (%)	11/85 (12.9)	2/48 (4.2)	7/98 (7.1)	3/46 (6.5)	18/183 (9.8)	5/94 (5.3)
2.non-White n/N2 (%)	5/56 (8.9)	3/24 (12.5)	8/46 (17.4)	1/26 (3.8)	13/102 (12.7)	4/50 (8.0)
Number of Patients with AE leading to study discontinuation						
1.White n/N1 (%)	5/85 (5.9)	0/48 (0.0)	3/98 (3.1)	3/46 (6.5)	8/183 (4.4)	3/94 (3.2)
2.non-White n/N2 (%)	3/56 (5.4)	2/24 (8.3)	4/46 (8.7)	0/26 (0.0)	7/102 (6.9)	2/50 (4.0)
Blood and lymphatic system disorders						
Anaemia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	0/183 (0.0)	1/94 (1.1)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Cardiac disorders						
Acute myocardial infarction						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	0/183 (0.0)	1/94 (1.1)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac arrest						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
Cardiac failure congestive						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Gastrointestinal disorders						
Nausea						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	1/98 (1.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Infections and infestations						
Pneumonia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Sepsis						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	0/183 (0.0)	1/94 (1.1)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Urosepsis						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Wound infection						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Injury, poisoning and procedural complications						
Fall						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	1/98 (1.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Multiple fractures						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Wound						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Blood creatinine increased						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
Metabolism and nutrition disorders						
Fluid overload						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Hypercalcaemia						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Musculoskeletal and connective tissue disorders						
Arthralgia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Muscular weakness						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	1/24 (4.2)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	1/50 (2.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Amnesia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Cerebrovascular accident						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	1/24 (4.2)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	1/50 (2.0)
Myasthenia gravis crisis						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	1/98 (1.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Psychiatric disorders						
Hallucination						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	1/24 (4.2)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	1/50 (2.0)
Respiratory, thoracic and mediastinal disorders						
Epistaxis						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.8365		0.8824		0.7458	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	50/71 (70.4)	28/36 (77.8)	49/80 (61.3)	21/35 (60.0)	99/151 (65.6)	49/71 (69.0)
RR [95%-CI]; p-value	0.91 [0.72, 1.14], 0.3986		1.02 [0.74, 1.41], 0.9001		0.95 [0.78, 1.15], 0.6043	
OR [95%-CI]; p-value	0.68 [0.27, 1.74], 0.4186		1.05 [0.47, 2.37], 0.8994		0.85 [0.47, 1.56], 0.6109	
RD [95%-CI]; p-value	-0.07 [-0.25, 0.10], 0.4030		0.01 [-0.18, 0.21], 0.8996		-0.03 [-0.17, 0.10], 0.6072	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	51/70 (72.9)	28/36 (77.8)	42/64 (65.6)	23/37 (62.2)	93/134 (69.4)	51/73 (69.9)
RR [95%-CI]; p-value	0.94 [0.75, 1.17], 0.5703		1.06 [0.78, 1.44], 0.7298		0.99 [0.82, 1.20], 0.9451	
OR [95%-CI]; p-value	0.77 [0.30, 1.98], 0.5819		1.16 [0.50, 2.69], 0.7263		0.98 [0.53, 1.82], 0.9452	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5731		0.03 [-0.16, 0.23], 0.7276		-0.00 [-0.14, 0.13], 0.9451	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.3489		0.5307		0.5028	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	7/36 (19.4)	9/80 (11.3)	0/35 (0.0)	17/151 (11.3)	7/71 (9.9)
RR [95%-CI]; p-value	0.58 [0.23, 1.47], 0.2511		7.99 [0.48, 134.03], 0.1487		1.14 [0.50, 2.63], 0.7551	
OR [95%-CI]; p-value	0.53 [0.17, 1.59], 0.2497		8.87 [0.50, 157.50], 0.0757		1.16 [0.46, 2.94], 0.7542	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2813		0.10 [0.02, 0.18], 0.0151		0.01 [-0.07, 0.10], 0.7491	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	4/36 (11.1)	10/64 (15.6)	2/37 (5.4)	19/134 (14.2)	6/73 (8.2)
RR [95%-CI]; p-value	1.16 [0.38, 3.50], 0.7961		2.89 [0.67, 12.49], 0.1551		1.73 [0.72, 4.13], 0.2206	
OR [95%-CI]; p-value	1.18 [0.34, 4.13], 0.7952		3.24 [0.67, 15.68], 0.1262		1.84 [0.70, 4.85], 0.2086	
RD [95%-CI]; p-value	0.02 [-0.11, 0.15], 0.7911		0.10 [-0.01, 0.22], 0.0815		0.06 [-0.03, 0.15], 0.1762	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.7917		0.3100		0.3596	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	4/80 (5.0)	4/35 (11.4)	12/151 (7.9)	7/71 (9.9)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		0.44 [0.12, 1.65], 0.2224		0.81 [0.33, 1.96], 0.6343	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		0.41 [0.10, 1.73], 0.2125		0.79 [0.30, 2.10], 0.6348	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		-0.06 [-0.18, 0.05], 0.2762		-0.02 [-0.10, 0.06], 0.6463	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	3/36 (8.3)	6/64 (9.4)	3/37 (8.1)	16/134 (11.9)	6/73 (8.2)
RR [95%-CI]; p-value	1.71 [0.50, 5.84], 0.3889		1.16 [0.31, 4.35], 0.8300		1.45 [0.59, 3.55], 0.4129	
OR [95%-CI]; p-value	1.83 [0.47, 7.13], 0.3763		1.17 [0.28, 4.99], 0.8295		1.51 [0.57, 4.05], 0.4065	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.3387		0.01 [-0.10, 0.13], 0.8265		0.04 [-0.05, 0.12], 0.3828	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.4398		0.8999		0.6087	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	14/71 (19.7)	7/36 (19.4)	12/80 (15.0)	5/35 (14.3)	26/151 (17.2)	12/71 (16.9)
RR [95%-CI]; p-value	1.01 [0.45, 2.29], 0.9731		1.05 [0.40, 2.76], 0.9210		1.02 [0.55, 1.90], 0.9534	
OR [95%-CI]; p-value	1.02 [0.37, 2.80], 0.9731		1.06 [0.34, 3.27], 0.9209		1.02 [0.48, 2.17], 0.9533	
RD [95%-CI]; p-value	0.00 [-0.16, 0.16], 0.9731		0.01 [-0.13, 0.15], 0.9203		0.00 [-0.10, 0.11], 0.9532	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	16/70 (22.9)	5/36 (13.9)	10/64 (15.6)	6/37 (16.2)	26/134 (19.4)	11/73 (15.1)
RR [95%-CI]; p-value	1.65 [0.66, 4.13], 0.2887		0.96 [0.38, 2.44], 0.9375		1.29 [0.68, 2.45], 0.4422	
OR [95%-CI]; p-value	1.84 [0.61, 5.50], 0.2726		0.96 [0.32, 2.89], 0.9375		1.36 [0.63, 2.93], 0.4367	
RD [95%-CI]; p-value	0.09 [-0.06, 0.24], 0.2406		-0.01 [-0.15, 0.14], 0.9378		0.04 [-0.06, 0.15], 0.4225	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.8889		0.3126		0.5530	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	7/71 (9.9)	2/36 (5.6)	8/80 (10.0)	3/35 (8.6)	15/151 (9.9)	5/71 (7.0)
RR [95%-CI]; p-value	1.77 [0.39, 8.11], 0.4594		1.17 [0.33, 4.14], 0.8114		1.41 [0.53, 3.73], 0.4879	
OR [95%-CI]; p-value	1.86 [0.37, 9.45], 0.4486		1.19 [0.29, 4.76], 0.8106		1.46 [0.51, 4.18], 0.4828	
RD [95%-CI]; p-value	0.04 [-0.06, 0.15], 0.4083		0.01 [-0.10, 0.13], 0.8054		0.03 [-0.05, 0.11], 0.4575	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	3/36 (8.3)	7/64 (10.9)	1/37 (2.7)	16/134 (11.9)	4/73 (5.5)
RR [95%-CI]; p-value	1.54 [0.45, 5.35], 0.4942		4.05 [0.52, 31.62], 0.1826		2.18 [0.76, 6.28], 0.1490	
OR [95%-CI]; p-value	1.62 [0.41, 6.41], 0.4863		4.42 [0.52, 37.44], 0.1398		2.34 [0.75, 7.28], 0.1328	
RD [95%-CI]; p-value	0.05 [-0.07, 0.16], 0.4584		0.08 [-0.01, 0.17], 0.0814		0.06 [-0.01, 0.14], 0.0946	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8700		0.1589		0.2331	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	0/36 (0.0)	3/80 (3.8)	3/35 (8.6)	5/151 (3.3)	3/71 (4.2)
RR [95%-CI]; p-value	2.06 [0.10, 44.44], 0.6457		0.44 [0.09, 2.06], 0.2959		0.78 [0.19, 3.19], 0.7335	
OR [95%-CI]; p-value	2.09 [0.09, 47.50], 0.6374		0.42 [0.08, 2.17], 0.2847		0.78 [0.18, 3.34], 0.7332	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5986		-0.05 [-0.15, 0.05], 0.3526		-0.01 [-0.06, 0.05], 0.7438	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	2/36 (5.6)	4/64 (6.3)	0/37 (0.0)	10/134 (7.5)	2/73 (2.7)
RR [95%-CI]; p-value	1.54 [0.33, 7.26], 0.5832		4.69 [0.25, 86.24], 0.2985		2.72 [0.61, 12.10], 0.1878	
OR [95%-CI]; p-value	1.59 [0.31, 8.33], 0.5777		4.93 [0.25, 96.00], 0.2454		2.86 [0.61, 13.43], 0.1647	
RD [95%-CI]; p-value	0.03 [-0.07, 0.13], 0.5524		0.05 [-0.02, 0.12], 0.1671		0.05 [-0.01, 0.11], 0.1114	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.5010		0.8894		0.3836	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	1/71 (1.4)	1/36 (2.8)	2/80 (2.5)	1/35 (2.9)	3/151 (2.0)	2/71 (2.8)
RR [95%-CI]; p-value	0.51 [0.03, 7.87], 0.6274		0.88 [0.08, 9.34], 0.9120		0.71 [0.12, 4.13], 0.6985	
OR [95%-CI]; p-value	0.50 [0.03, 8.23], 0.6212		0.87 [0.08, 9.94], 0.9120		0.70 [0.11, 4.28], 0.6974	
RD [95%-CI]; p-value	-0.01 [-0.07, 0.05], 0.6561		-0.00 [-0.07, 0.06], 0.9142		-0.01 [-0.05, 0.04], 0.7144	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	1/64 (1.6)	0/37 (0.0)	3/134 (2.2)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		1.17 [0.04, 34.10], 0.9265		3.29 [0.17, 64.82], 0.4334	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		1.17 [0.04, 35.87], 0.9264		3.34 [0.17, 67.67], 0.4044	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.00 [-0.05, 0.05], 0.9249		0.02 [-0.02, 0.05], 0.3293	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.5551		0.4596		0.3124	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	42/71 (59.2)	27/36 (75.0)	39/80 (48.8)	19/35 (54.3)	81/151 (53.6)	46/71 (64.8)
RR [95%-CI]; p-value	0.79 [0.60, 1.03], 0.0850		0.90 [0.62, 1.31], 0.5771		0.83 [0.66, 1.04], 0.1026	
OR [95%-CI]; p-value	0.48 [0.20, 1.18], 0.1056		0.80 [0.36, 1.78], 0.5848		0.63 [0.35, 1.13], 0.1175	
RD [95%-CI]; p-value	-0.16 [-0.34, 0.02], 0.0877		-0.06 [-0.25, 0.14], 0.5839		-0.11 [-0.25, 0.03], 0.1098	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	40/70 (57.1)	23/36 (63.9)	31/64 (48.4)	16/37 (43.2)	71/134 (53.0)	39/73 (53.4)
RR [95%-CI]; p-value	0.89 [0.65, 1.23], 0.4923		1.12 [0.72, 1.75], 0.6192		0.99 [0.76, 1.30], 0.9516	
OR [95%-CI]; p-value	0.75 [0.33, 1.73], 0.5029		1.23 [0.55, 2.78], 0.6141		0.98 [0.55, 1.74], 0.9517	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.13], 0.4979		0.05 [-0.15, 0.25], 0.6128		-0.00 [-0.15, 0.14], 0.9517	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.7129		0.0466		0.1167	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	26/71 (36.6)	14/36 (38.9)	29/80 (36.3)	5/35 (14.3)	55/151 (36.4)	19/71 (26.8)
RR [95%-CI]; p-value	0.94 [0.56, 1.57], 0.8177		2.54 [1.07, 6.01], 0.0342		1.36 [0.88, 2.11], 0.1684	
OR [95%-CI]; p-value	0.91 [0.40, 2.07], 0.8187		3.41 [1.19, 9.76], 0.0175		1.57 [0.84, 2.92], 0.1543	
RD [95%-CI]; p-value	-0.02 [-0.22, 0.17], 0.8193		0.22 [0.06, 0.38], 0.0060		0.10 [-0.03, 0.23], 0.1403	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	24/70 (34.3)	15/36 (41.7)	20/64 (31.3)	13/37 (35.1)	44/134 (32.8)	28/73 (38.4)
RR [95%-CI]; p-value	0.82 [0.50, 1.36], 0.4488		0.89 [0.50, 1.57], 0.6865		0.86 [0.59, 1.25], 0.4209	
OR [95%-CI]; p-value	0.73 [0.32, 1.67], 0.4555		0.84 [0.36, 1.98], 0.6884		0.79 [0.43, 1.42], 0.4256	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.12], 0.4598		-0.04 [-0.23, 0.15], 0.6904		-0.06 [-0.19, 0.08], 0.4296	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.7917		0.3100		0.3596	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	4/80 (5.0)	4/35 (11.4)	12/151 (7.9)	7/71 (9.9)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		0.44 [0.12, 1.65], 0.2224		0.81 [0.33, 1.96], 0.6343	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		0.41 [0.10, 1.73], 0.2125		0.79 [0.30, 2.10], 0.6348	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		-0.06 [-0.18, 0.05], 0.2762		-0.02 [-0.10, 0.06], 0.6463	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	3/36 (8.3)	6/64 (9.4)	3/37 (8.1)	16/134 (11.9)	6/73 (8.2)
RR [95%-CI]; p-value	1.71 [0.50, 5.84], 0.3889		1.16 [0.31, 4.35], 0.8300		1.45 [0.59, 3.55], 0.4129	
OR [95%-CI]; p-value	1.83 [0.47, 7.13], 0.3763		1.17 [0.28, 4.99], 0.8295		1.51 [0.57, 4.05], 0.4065	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.3387		0.01 [-0.10, 0.13], 0.8265		0.04 [-0.05, 0.12], 0.3828	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6240		0.1690		0.1759	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	5/71 (7.0)	5/36 (13.9)	6/80 (7.5)	4/35 (11.4)	11/151 (7.3)	9/71 (12.7)
RR [95%-CI]; p-value	0.51 [0.16, 1.64], 0.2564		0.66 [0.20, 2.18], 0.4919		0.57 [0.25, 1.32], 0.1933	
OR [95%-CI]; p-value	0.47 [0.13, 1.74], 0.2503		0.63 [0.17, 2.38], 0.4915		0.54 [0.21, 1.37], 0.1907	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.06], 0.2933		-0.04 [-0.16, 0.08], 0.5217		-0.05 [-0.14, 0.03], 0.2287	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	4/36 (11.1)	5/64 (7.8)	0/37 (0.0)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	0.77 [0.23, 2.56], 0.6716		5.86 [0.33, 104.28], 0.2287		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	0.75 [0.20, 2.85], 0.6718		6.27 [0.33, 118.15], 0.1640		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.10], 0.6828		0.06 [-0.01, 0.14], 0.0917		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.5931		0.1047		0.1613	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	16/71 (22.5)	10/36 (27.8)	18/80 (22.5)	2/35 (5.7)	34/151 (22.5)	12/71 (16.9)
RR [95%-CI]; p-value	0.81 [0.41, 1.60], 0.5470		3.94 [0.97, 16.06], 0.0560		1.33 [0.74, 2.41], 0.3444	
OR [95%-CI]; p-value	0.76 [0.30, 1.89], 0.5502		4.79 [1.05, 21.92], 0.0289		1.43 [0.69, 2.96], 0.3357	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.12], 0.5586		0.17 [0.05, 0.29], 0.0059		0.06 [-0.05, 0.17], 0.3158	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	10/36 (27.8)	8/64 (12.5)	5/37 (13.5)	20/134 (14.9)	15/73 (20.5)
RR [95%-CI]; p-value	0.62 [0.30, 1.29], 0.1991		0.93 [0.33, 2.62], 0.8834		0.73 [0.40, 1.33], 0.3009	
OR [95%-CI]; p-value	0.54 [0.21, 1.40], 0.2010		0.91 [0.28, 3.03], 0.8835		0.68 [0.32, 1.42], 0.3025	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.2226		-0.01 [-0.15, 0.13], 0.8845		-0.06 [-0.17, 0.05], 0.3190	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9463		0.7196		0.8727	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	10/71 (14.1)	8/36 (22.2)	10/80 (12.5)	5/35 (14.3)	20/151 (13.2)	13/71 (18.3)
RR [95%-CI]; p-value	0.63 [0.27, 1.47], 0.2866		0.88 [0.32, 2.37], 0.7930		0.72 [0.38, 1.37], 0.3204	
OR [95%-CI]; p-value	0.57 [0.20, 1.61], 0.2877		0.86 [0.27, 2.72], 0.7936		0.68 [0.32, 1.46], 0.3225	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3130		-0.02 [-0.15, 0.12], 0.7980		-0.05 [-0.16, 0.05], 0.3442	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	7/36 (19.4)	7/64 (10.9)	6/37 (16.2)	16/134 (11.9)	13/73 (17.8)
RR [95%-CI]; p-value	0.66 [0.27, 1.63], 0.3689		0.67 [0.25, 1.86], 0.4459		0.67 [0.34, 1.32], 0.2451	
OR [95%-CI]; p-value	0.61 [0.21, 1.80], 0.3696		0.63 [0.20, 2.05], 0.4453		0.63 [0.28, 1.39], 0.2452	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.09], 0.3932		-0.05 [-0.19, 0.09], 0.4639		-0.06 [-0.16, 0.04], 0.2666	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9759		0.1504		0.3498	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	19/71 (26.8)	10/36 (27.8)	23/80 (28.8)	7/35 (20.0)	42/151 (27.8)	17/71 (23.9)
RR [95%-CI]; p-value	0.96 [0.50, 1.85], 0.9107		1.44 [0.68, 3.03], 0.3410		1.16 [0.71, 1.89], 0.5470	
OR [95%-CI]; p-value	0.95 [0.39, 2.33], 0.9109		1.61 [0.62, 4.21], 0.3255		1.22 [0.64, 2.35], 0.5426	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9113		0.09 [-0.08, 0.25], 0.3002		0.04 [-0.08, 0.16], 0.5351	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	19/70 (27.1)	10/36 (27.8)	10/64 (15.6)	9/37 (24.3)	29/134 (21.6)	19/73 (26.0)
RR [95%-CI]; p-value	0.98 [0.51, 1.87], 0.9446		0.64 [0.29, 1.44], 0.2809		0.83 [0.50, 1.38], 0.4724	
OR [95%-CI]; p-value	0.97 [0.39, 2.38], 0.9446		0.58 [0.21, 1.58], 0.2811		0.78 [0.40, 1.53], 0.4750	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9448		-0.09 [-0.25, 0.08], 0.2997		-0.04 [-0.17, 0.08], 0.4827	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.5883		0.4690		0.9958	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	7/80 (8.8)	1/35 (2.9)	15/151 (9.9)	4/71 (5.6)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		3.06 [0.39, 23.96], 0.2863		1.76 [0.61, 5.12], 0.2972	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		3.26 [0.39, 27.56], 0.2531		1.85 [0.59, 5.78], 0.2854	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		0.06 [-0.02, 0.14], 0.1638		0.04 [-0.03, 0.11], 0.2404	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	2/36 (5.6)	4/64 (6.3)	2/37 (5.4)	13/134 (9.7)	4/73 (5.5)
RR [95%-CI]; p-value	2.31 [0.53, 10.15], 0.2660		1.16 [0.22, 6.01], 0.8629		1.77 [0.60, 5.23], 0.3015	
OR [95%-CI]; p-value	2.51 [0.51, 12.28], 0.2431		1.17 [0.20, 6.70], 0.8626		1.85 [0.58, 5.91], 0.2905	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.1867		0.01 [-0.09, 0.10], 0.8601		0.04 [-0.03, 0.11], 0.2528	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.8590		0.3315		0.6335	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	5/36 (13.9)	8/80 (10.0)	2/35 (5.7)	16/151 (10.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.81 [0.29, 2.30], 0.6943		1.75 [0.39, 7.83], 0.4640		1.07 [0.46, 2.50], 0.8668	
OR [95%-CI]; p-value	0.79 [0.24, 2.61], 0.6949		1.83 [0.37, 9.11], 0.4529		1.08 [0.42, 2.76], 0.8666	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7031		0.04 [-0.06, 0.14], 0.4064		0.01 [-0.08, 0.09], 0.8650	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	5/36 (13.9)	6/64 (9.4)	5/37 (13.5)	15/134 (11.2)	10/73 (13.7)
RR [95%-CI]; p-value	0.93 [0.33, 2.56], 0.8817		0.69 [0.23, 2.12], 0.5206		0.82 [0.39, 1.73], 0.5966	
OR [95%-CI]; p-value	0.91 [0.28, 2.96], 0.8819		0.66 [0.19, 2.34], 0.5201		0.79 [0.34, 1.87], 0.5972	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.13], 0.8831		-0.04 [-0.17, 0.09], 0.5367		-0.03 [-0.12, 0.07], 0.6063	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.4296		0.0708		0.0651	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	12/71 (16.9)	11/36 (30.6)	10/80 (12.5)	8/35 (22.9)	22/151 (14.6)	19/71 (26.8)
RR [95%-CI]; p-value	0.55 [0.27, 1.13], 0.1036		0.55 [0.24, 1.27], 0.1593		0.54 [0.32, 0.94], 0.0288	
OR [95%-CI]; p-value	0.46 [0.18, 1.19], 0.1043		0.48 [0.17, 1.35], 0.1596		0.47 [0.23, 0.93], 0.0290	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1238		-0.10 [-0.26, 0.05], 0.1956		-0.12 [-0.24, -0.00], 0.0417	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	16/70 (22.9)	10/36 (27.8)	15/64 (23.4)	5/37 (13.5)	31/134 (23.1)	15/73 (20.5)
RR [95%-CI]; p-value	0.82 [0.42, 1.62], 0.5742		1.73 [0.69, 4.39], 0.2447		1.13 [0.65, 1.94], 0.6707	
OR [95%-CI]; p-value	0.77 [0.31, 1.93], 0.5771		1.96 [0.65, 5.92], 0.2279		1.16 [0.58, 2.33], 0.6689	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.5844		0.10 [-0.05, 0.25], 0.1987		0.03 [-0.09, 0.14], 0.6648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4237		0.4432		0.3282	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	14/71 (19.7)	11/36 (30.6)	12/80 (15.0)	5/35 (14.3)	26/151 (17.2)	16/71 (22.5)
RR [95%-CI]; p-value	0.65 [0.33, 1.27], 0.2070		1.05 [0.40, 2.76], 0.9210		0.76 [0.44, 1.33], 0.3422	
OR [95%-CI]; p-value	0.56 [0.22, 1.40], 0.2107		1.06 [0.34, 3.27], 0.9209		0.72 [0.36, 1.44], 0.3455	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2292		0.01 [-0.13, 0.15], 0.9203		-0.05 [-0.17, 0.06], 0.3621	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	12/36 (33.3)	10/64 (15.6)	9/37 (24.3)	20/134 (14.9)	21/73 (28.8)
RR [95%-CI]; p-value	0.43 [0.21, 0.90], 0.0242		0.64 [0.29, 1.44], 0.2809		0.52 [0.30, 0.89], 0.0176	
OR [95%-CI]; p-value	0.33 [0.13, 0.87], 0.0220		0.58 [0.21, 1.58], 0.2811		0.43 [0.22, 0.87], 0.0170	
RD [95%-CI]; p-value	-0.19 [-0.36, -0.02], 0.0324		-0.09 [-0.25, 0.08], 0.2997		-0.14 [-0.26, -0.02], 0.0239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
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N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.5274		0.1683		0.1823	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	7/71 (9.9)	6/36 (16.7)	12/80 (15.0)	2/35 (5.7)	19/151 (12.6)	8/71 (11.3)
RR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3102		2.63 [0.62, 11.12], 0.1900		1.12 [0.51, 2.43], 0.7805	
OR [95%-CI]; p-value	0.55 [0.17, 1.77], 0.3085		2.91 [0.62, 13.77], 0.1611		1.13 [0.47, 2.73], 0.7798	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3409		0.09 [-0.02, 0.20], 0.0971		0.01 [-0.08, 0.10], 0.7760	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	7/36 (19.4)	8/64 (12.5)	6/37 (16.2)	13/134 (9.7)	13/73 (17.8)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0679		0.77 [0.29, 2.05], 0.6020		0.54 [0.27, 1.11], 0.0954	
OR [95%-CI]; p-value	0.32 [0.09, 1.09], 0.0584		0.74 [0.23, 2.32], 0.6025		0.50 [0.22, 1.14], 0.0926	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.02], 0.0910		-0.04 [-0.18, 0.11], 0.6124		-0.08 [-0.18, 0.02], 0.1159	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4095		0.3057		0.9116	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	7/36 (19.4)	14/80 (17.5)	4/35 (11.4)	22/151 (14.6)	11/71 (15.5)
RR [95%-CI]; p-value	0.58 [0.23, 1.47], 0.2511		1.53 [0.54, 4.32], 0.4210		0.94 [0.48, 1.83], 0.8566	
OR [95%-CI]; p-value	0.53 [0.17, 1.59], 0.2497		1.64 [0.50, 5.41], 0.4096		0.93 [0.42, 2.04], 0.8568	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2813		0.06 [-0.07, 0.20], 0.3757		-0.01 [-0.11, 0.09], 0.8581	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	5/36 (13.9)	3/64 (4.7)	3/37 (8.1)	13/134 (9.7)	8/73 (11.0)
RR [95%-CI]; p-value	1.03 [0.38, 2.78], 0.9558		0.58 [0.12, 2.72], 0.4879		0.89 [0.38, 2.04], 0.7744	
OR [95%-CI]; p-value	1.03 [0.32, 3.29], 0.9557		0.56 [0.11, 2.91], 0.4835		0.87 [0.34, 2.21], 0.7747	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 0.9556		-0.03 [-0.14, 0.07], 0.5113		-0.01 [-0.10, 0.07], 0.7781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.2987		0.3988		0.8859	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	9/80 (11.3)	2/35 (5.7)	11/151 (7.3)	6/71 (8.5)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		1.97 [0.45, 8.65], 0.3696		0.86 [0.33, 2.24], 0.7603	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		2.09 [0.43, 10.22], 0.3530		0.85 [0.30, 2.40], 0.7606	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.06 [-0.05, 0.16], 0.2944		-0.01 [-0.09, 0.07], 0.7662	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	7/70 (10.0)	5/36 (13.9)	6/64 (9.4)	4/37 (10.8)	13/134 (9.7)	9/73 (12.3)
RR [95%-CI]; p-value	0.72 [0.25, 2.11], 0.5492		0.87 [0.26, 2.88], 0.8158		0.79 [0.35, 1.75], 0.5574	
OR [95%-CI]; p-value	0.69 [0.20, 2.35], 0.5495		0.85 [0.22, 3.24], 0.8159		0.76 [0.31, 1.88], 0.5579	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5667		-0.01 [-0.14, 0.11], 0.8189		-0.03 [-0.12, 0.06], 0.5696	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4231		0.9943		0.5100	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	5/36 (13.9)	7/80 (8.8)	4/35 (11.4)	13/151 (8.6)	9/71 (12.7)
RR [95%-CI]; p-value	0.61 [0.20, 1.86], 0.3833		0.77 [0.24, 2.45], 0.6525		0.68 [0.30, 1.51], 0.3443	
OR [95%-CI]; p-value	0.57 [0.16, 2.02], 0.3815		0.74 [0.20, 2.72], 0.6532		0.65 [0.26, 1.60], 0.3442	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4129		-0.03 [-0.15, 0.10], 0.6676		-0.04 [-0.13, 0.05], 0.3726	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	4/36 (11.1)	4/64 (6.3)	3/37 (8.1)	13/134 (9.7)	7/73 (9.6)
RR [95%-CI]; p-value	1.16 [0.38, 3.50], 0.7961		0.77 [0.18, 3.26], 0.7234		1.01 [0.42, 2.42], 0.9791	
OR [95%-CI]; p-value	1.18 [0.34, 4.13], 0.7952		0.76 [0.16, 3.58], 0.7232		1.01 [0.39, 2.66], 0.9791	
RD [95%-CI]; p-value	0.02 [-0.11, 0.15], 0.7911		-0.02 [-0.12, 0.09], 0.7314		0.00 [-0.08, 0.09], 0.9791	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.3.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9889		0.5561		0.2832	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	5/80 (6.3)	0/35 (0.0)	7/151 (4.6)	4/71 (5.6)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		4.44 [0.25, 79.06], 0.3106		0.82 [0.25, 2.72], 0.7493	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		4.67 [0.25, 87.80], 0.2596		0.81 [0.23, 2.88], 0.7493	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.05 [-0.02, 0.11], 0.1486		-0.01 [-0.07, 0.05], 0.7571	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	8/36 (22.2)	1/64 (1.6)	0/37 (0.0)	5/134 (3.7)	8/73 (11.0)
RR [95%-CI]; p-value	0.26 [0.08, 0.80], 0.0186		1.17 [0.04, 34.10], 0.9265		0.34 [0.12, 1.00], 0.0506	
OR [95%-CI]; p-value	0.21 [0.06, 0.76], 0.0111		1.17 [0.04, 35.87], 0.9264		0.31 [0.10, 1.00], 0.0406	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0270		0.00 [-0.05, 0.05], 0.9249		-0.07 [-0.15, 0.01], 0.0712	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_3_m_pt_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.3.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4599		0.6195		0.6854	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	6/36 (16.7)	4/80 (5.0)	1/35 (2.9)	7/151 (4.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.25 [0.07, 0.96], 0.0426		1.75 [0.20, 15.10], 0.6108		0.47 [0.17, 1.29], 0.1427	
OR [95%-CI]; p-value	0.22 [0.05, 0.94], 0.0285		1.79 [0.19, 16.61], 0.6041		0.44 [0.15, 1.32], 0.1354	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0615		0.02 [-0.05, 0.09], 0.5650		-0.05 [-0.13, 0.02], 0.1838	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	4/36 (11.1)	3/64 (4.7)	2/37 (5.4)	7/134 (5.2)	6/73 (8.2)
RR [95%-CI]; p-value	0.51 [0.14, 1.94], 0.3258		0.87 [0.15, 4.95], 0.8727		0.64 [0.22, 1.82], 0.3987	
OR [95%-CI]; p-value	0.48 [0.11, 2.06], 0.3192		0.86 [0.14, 5.40], 0.8727		0.62 [0.20, 1.91], 0.3960	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3625		-0.01 [-0.10, 0.08], 0.8749		-0.03 [-0.10, 0.04], 0.4239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_3_m_pt_ae10pct_ckd.sas using SAS 9.4

Table 12.4.8.1.1.s5
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.3830		0.9952		0.5265	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	2/36 (5.6)	2/80 (2.5)	1/35 (2.9)	5/151 (3.3)	3/71 (4.2)
RR [95%-CI]; p-value	0.76 [0.13, 4.35], 0.7584		0.88 [0.08, 9.34], 0.9120		0.78 [0.19, 3.19], 0.7335	
OR [95%-CI]; p-value	0.75 [0.12, 4.70], 0.7581		0.87 [0.08, 9.94], 0.9120		0.78 [0.18, 3.34], 0.7332	
RD [95%-CI]; p-value	-0.01 [-0.10, 0.07], 0.7677		-0.00 [-0.07, 0.06], 0.9142		-0.01 [-0.06, 0.05], 0.7438	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	1/36 (2.8)	3/64 (4.7)	2/37 (5.4)	8/134 (6.0)	3/73 (4.1)
RR [95%-CI]; p-value	2.57 [0.31, 21.19], 0.3801		0.87 [0.15, 4.95], 0.8727		1.45 [0.40, 5.31], 0.5722	
OR [95%-CI]; p-value	2.69 [0.30, 23.96], 0.3570		0.86 [0.14, 5.40], 0.8727		1.48 [0.38, 5.76], 0.5685	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.2894		-0.01 [-0.10, 0.08], 0.8749		0.02 [-0.04, 0.08], 0.5479	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_8_1_1_m_soc_sae5pct_ckd.sas using SAS 9.4

Table 12.4.8.1.2.s5
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_8_1_2_m_pt_sae5pct_ckd.sas using SAS 9.4

Table 12.4.5.1.1.s5
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_5_1_1_m_soc_aeg35pct_ckd.sas using SAS 9.4

Table 12.4.5.1.2.s5
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_5_1_2_m_pt_aeg35pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6240		0.1690		0.1759	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	5/71 (7.0)	5/36 (13.9)	6/80 (7.5)	4/35 (11.4)	11/151 (7.3)	9/71 (12.7)
RR [95%-CI]; p-value	0.51 [0.16, 1.64], 0.2564		0.66 [0.20, 2.18], 0.4919		0.57 [0.25, 1.32], 0.1933	
OR [95%-CI]; p-value	0.47 [0.13, 1.74], 0.2503		0.63 [0.17, 2.38], 0.4915		0.54 [0.21, 1.37], 0.1907	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.06], 0.2933		-0.04 [-0.16, 0.08], 0.5217		-0.05 [-0.14, 0.03], 0.2287	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	4/36 (11.1)	5/64 (7.8)	0/37 (0.0)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	0.77 [0.23, 2.56], 0.6716		5.86 [0.33, 104.28], 0.2287		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	0.75 [0.20, 2.85], 0.6718		6.27 [0.33, 118.15], 0.1640		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.10], 0.6828		0.06 [-0.01, 0.14], 0.0917		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.5931		0.1047		0.1613	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	16/71 (22.5)	10/36 (27.8)	18/80 (22.5)	2/35 (5.7)	34/151 (22.5)	12/71 (16.9)
RR [95%-CI]; p-value	0.81 [0.41, 1.60], 0.5470		3.94 [0.97, 16.06], 0.0560		1.33 [0.74, 2.41], 0.3444	
OR [95%-CI]; p-value	0.76 [0.30, 1.89], 0.5502		4.79 [1.05, 21.92], 0.0289		1.43 [0.69, 2.96], 0.3357	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.12], 0.5586		0.17 [0.05, 0.29], 0.0059		0.06 [-0.05, 0.17], 0.3158	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	10/36 (27.8)	8/64 (12.5)	5/37 (13.5)	20/134 (14.9)	15/73 (20.5)
RR [95%-CI]; p-value	0.62 [0.30, 1.29], 0.1991		0.93 [0.33, 2.62], 0.8834		0.73 [0.40, 1.33], 0.3009	
OR [95%-CI]; p-value	0.54 [0.21, 1.40], 0.2010		0.91 [0.28, 3.03], 0.8835		0.68 [0.32, 1.42], 0.3025	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.2226		-0.01 [-0.15, 0.13], 0.8845		-0.06 [-0.17, 0.05], 0.3190	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9463		0.7196		0.8727	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	10/71 (14.1)	8/36 (22.2)	10/80 (12.5)	5/35 (14.3)	20/151 (13.2)	13/71 (18.3)
RR [95%-CI]; p-value	0.63 [0.27, 1.47], 0.2866		0.88 [0.32, 2.37], 0.7930		0.72 [0.38, 1.37], 0.3204	
OR [95%-CI]; p-value	0.57 [0.20, 1.61], 0.2877		0.86 [0.27, 2.72], 0.7936		0.68 [0.32, 1.46], 0.3225	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3130		-0.02 [-0.15, 0.12], 0.7980		-0.05 [-0.16, 0.05], 0.3442	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	7/36 (19.4)	7/64 (10.9)	6/37 (16.2)	16/134 (11.9)	13/73 (17.8)
RR [95%-CI]; p-value	0.66 [0.27, 1.63], 0.3689		0.67 [0.25, 1.86], 0.4459		0.67 [0.34, 1.32], 0.2451	
OR [95%-CI]; p-value	0.61 [0.21, 1.80], 0.3696		0.63 [0.20, 2.05], 0.4453		0.63 [0.28, 1.39], 0.2452	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.09], 0.3932		-0.05 [-0.19, 0.09], 0.4639		-0.06 [-0.16, 0.04], 0.2666	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9759		0.1504		0.3498	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	19/71 (26.8)	10/36 (27.8)	23/80 (28.8)	7/35 (20.0)	42/151 (27.8)	17/71 (23.9)
RR [95%-CI]; p-value	0.96 [0.50, 1.85], 0.9107		1.44 [0.68, 3.03], 0.3410		1.16 [0.71, 1.89], 0.5470	
OR [95%-CI]; p-value	0.95 [0.39, 2.33], 0.9109		1.61 [0.62, 4.21], 0.3255		1.22 [0.64, 2.35], 0.5426	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9113		0.09 [-0.08, 0.25], 0.3002		0.04 [-0.08, 0.16], 0.5351	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	19/70 (27.1)	10/36 (27.8)	10/64 (15.6)	9/37 (24.3)	29/134 (21.6)	19/73 (26.0)
RR [95%-CI]; p-value	0.98 [0.51, 1.87], 0.9446		0.64 [0.29, 1.44], 0.2809		0.83 [0.50, 1.38], 0.4724	
OR [95%-CI]; p-value	0.97 [0.39, 2.38], 0.9446		0.58 [0.21, 1.58], 0.2811		0.78 [0.40, 1.53], 0.4750	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9448		-0.09 [-0.25, 0.08], 0.2997		-0.04 [-0.17, 0.08], 0.4827	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.5883		0.4690		0.9958	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	7/80 (8.8)	1/35 (2.9)	15/151 (9.9)	4/71 (5.6)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		3.06 [0.39, 23.96], 0.2863		1.76 [0.61, 5.12], 0.2972	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		3.26 [0.39, 27.56], 0.2531		1.85 [0.59, 5.78], 0.2854	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		0.06 [-0.02, 0.14], 0.1638		0.04 [-0.03, 0.11], 0.2404	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	2/36 (5.6)	4/64 (6.3)	2/37 (5.4)	13/134 (9.7)	4/73 (5.5)
RR [95%-CI]; p-value	2.31 [0.53, 10.15], 0.2660		1.16 [0.22, 6.01], 0.8629		1.77 [0.60, 5.23], 0.3015	
OR [95%-CI]; p-value	2.51 [0.51, 12.28], 0.2431		1.17 [0.20, 6.70], 0.8626		1.85 [0.58, 5.91], 0.2905	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.1867		0.01 [-0.09, 0.10], 0.8601		0.04 [-0.03, 0.11], 0.2528	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.8590		0.3315		0.6335	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	5/36 (13.9)	8/80 (10.0)	2/35 (5.7)	16/151 (10.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.81 [0.29, 2.30], 0.6943		1.75 [0.39, 7.83], 0.4640		1.07 [0.46, 2.50], 0.8668	
OR [95%-CI]; p-value	0.79 [0.24, 2.61], 0.6949		1.83 [0.37, 9.11], 0.4529		1.08 [0.42, 2.76], 0.8666	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7031		0.04 [-0.06, 0.14], 0.4064		0.01 [-0.08, 0.09], 0.8650	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	5/36 (13.9)	6/64 (9.4)	5/37 (13.5)	15/134 (11.2)	10/73 (13.7)
RR [95%-CI]; p-value	0.93 [0.33, 2.56], 0.8817		0.69 [0.23, 2.12], 0.5206		0.82 [0.39, 1.73], 0.5966	
OR [95%-CI]; p-value	0.91 [0.28, 2.96], 0.8819		0.66 [0.19, 2.34], 0.5201		0.79 [0.34, 1.87], 0.5972	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.13], 0.8831		-0.04 [-0.17, 0.09], 0.5367		-0.03 [-0.12, 0.07], 0.6063	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.4296		0.0708		0.0651	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	12/71 (16.9)	11/36 (30.6)	10/80 (12.5)	8/35 (22.9)	22/151 (14.6)	19/71 (26.8)
RR [95%-CI]; p-value	0.55 [0.27, 1.13], 0.1036		0.55 [0.24, 1.27], 0.1593		0.54 [0.32, 0.94], 0.0288	
OR [95%-CI]; p-value	0.46 [0.18, 1.19], 0.1043		0.48 [0.17, 1.35], 0.1596		0.47 [0.23, 0.93], 0.0290	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1238		-0.10 [-0.26, 0.05], 0.1956		-0.12 [-0.24, -0.00], 0.0417	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	16/70 (22.9)	10/36 (27.8)	15/64 (23.4)	5/37 (13.5)	31/134 (23.1)	15/73 (20.5)
RR [95%-CI]; p-value	0.82 [0.42, 1.62], 0.5742		1.73 [0.69, 4.39], 0.2447		1.13 [0.65, 1.94], 0.6707	
OR [95%-CI]; p-value	0.77 [0.31, 1.93], 0.5771		1.96 [0.65, 5.92], 0.2279		1.16 [0.58, 2.33], 0.6689	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.5844		0.10 [-0.05, 0.25], 0.1987		0.03 [-0.09, 0.14], 0.6648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4237		0.4432		0.3282	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	14/71 (19.7)	11/36 (30.6)	12/80 (15.0)	5/35 (14.3)	26/151 (17.2)	16/71 (22.5)
RR [95%-CI]; p-value	0.65 [0.33, 1.27], 0.2070		1.05 [0.40, 2.76], 0.9210		0.76 [0.44, 1.33], 0.3422	
OR [95%-CI]; p-value	0.56 [0.22, 1.40], 0.2107		1.06 [0.34, 3.27], 0.9209		0.72 [0.36, 1.44], 0.3455	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2292		0.01 [-0.13, 0.15], 0.9203		-0.05 [-0.17, 0.06], 0.3621	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	12/36 (33.3)	10/64 (15.6)	9/37 (24.3)	20/134 (14.9)	21/73 (28.8)
RR [95%-CI]; p-value	0.43 [0.21, 0.90], 0.0242		0.64 [0.29, 1.44], 0.2809		0.52 [0.30, 0.89], 0.0176	
OR [95%-CI]; p-value	0.33 [0.13, 0.87], 0.0220		0.58 [0.21, 1.58], 0.2811		0.43 [0.22, 0.87], 0.0170	
RD [95%-CI]; p-value	-0.19 [-0.36, -0.02], 0.0324		-0.09 [-0.25, 0.08], 0.2997		-0.14 [-0.26, -0.02], 0.0239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.5274		0.1683		0.1823	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	7/71 (9.9)	6/36 (16.7)	12/80 (15.0)	2/35 (5.7)	19/151 (12.6)	8/71 (11.3)
RR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3102		2.63 [0.62, 11.12], 0.1900		1.12 [0.51, 2.43], 0.7805	
OR [95%-CI]; p-value	0.55 [0.17, 1.77], 0.3085		2.91 [0.62, 13.77], 0.1611		1.13 [0.47, 2.73], 0.7798	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3409		0.09 [-0.02, 0.20], 0.0971		0.01 [-0.08, 0.10], 0.7760	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	7/36 (19.4)	8/64 (12.5)	6/37 (16.2)	13/134 (9.7)	13/73 (17.8)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0679		0.77 [0.29, 2.05], 0.6020		0.54 [0.27, 1.11], 0.0954	
OR [95%-CI]; p-value	0.32 [0.09, 1.09], 0.0584		0.74 [0.23, 2.32], 0.6025		0.50 [0.22, 1.14], 0.0926	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.02], 0.0910		-0.04 [-0.18, 0.11], 0.6124		-0.08 [-0.18, 0.02], 0.1159	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.0681		0.4528		0.2902	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	4/71 (5.6)	5/36 (13.9)	8/80 (10.0)	3/35 (8.6)	12/151 (7.9)	8/71 (11.3)
RR [95%-CI]; p-value	0.41 [0.12, 1.42], 0.1578		1.17 [0.33, 4.14], 0.8114		0.71 [0.30, 1.65], 0.4202	
OR [95%-CI]; p-value	0.37 [0.09, 1.47], 0.1460		1.19 [0.29, 4.76], 0.8106		0.68 [0.26, 1.75], 0.4203	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1957		0.01 [-0.10, 0.13], 0.8054		-0.03 [-0.12, 0.05], 0.4453	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	7/70 (10.0)	0/36 (0.0)	4/64 (6.3)	4/37 (10.8)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	7.30 [0.43, 125.08], 0.1703		0.58 [0.15, 2.18], 0.4178		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	8.00 [0.44, 145.13], 0.0985		0.55 [0.13, 2.34], 0.4135		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	0.09 [0.01, 0.17], 0.0339		-0.05 [-0.16, 0.07], 0.4422		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4095		0.3057		0.9116	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	7/36 (19.4)	14/80 (17.5)	4/35 (11.4)	22/151 (14.6)	11/71 (15.5)
RR [95%-CI]; p-value	0.58 [0.23, 1.47], 0.2511		1.53 [0.54, 4.32], 0.4210		0.94 [0.48, 1.83], 0.8566	
OR [95%-CI]; p-value	0.53 [0.17, 1.59], 0.2497		1.64 [0.50, 5.41], 0.4096		0.93 [0.42, 2.04], 0.8568	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2813		0.06 [-0.07, 0.20], 0.3757		-0.01 [-0.11, 0.09], 0.8581	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	5/36 (13.9)	3/64 (4.7)	3/37 (8.1)	13/134 (9.7)	8/73 (11.0)
RR [95%-CI]; p-value	1.03 [0.38, 2.78], 0.9558		0.58 [0.12, 2.72], 0.4879		0.89 [0.38, 2.04], 0.7744	
OR [95%-CI]; p-value	1.03 [0.32, 3.29], 0.9557		0.56 [0.11, 2.91], 0.4835		0.87 [0.34, 2.21], 0.7747	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 0.9556		-0.03 [-0.14, 0.07], 0.5113		-0.01 [-0.10, 0.07], 0.7781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.2987		0.3988		0.8859	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	9/80 (11.3)	2/35 (5.7)	11/151 (7.3)	6/71 (8.5)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		1.97 [0.45, 8.65], 0.3696		0.86 [0.33, 2.24], 0.7603	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		2.09 [0.43, 10.22], 0.3530		0.85 [0.30, 2.40], 0.7606	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.06 [-0.05, 0.16], 0.2944		-0.01 [-0.09, 0.07], 0.7662	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	7/70 (10.0)	5/36 (13.9)	6/64 (9.4)	4/37 (10.8)	13/134 (9.7)	9/73 (12.3)
RR [95%-CI]; p-value	0.72 [0.25, 2.11], 0.5492		0.87 [0.26, 2.88], 0.8158		0.79 [0.35, 1.75], 0.5574	
OR [95%-CI]; p-value	0.69 [0.20, 2.35], 0.5495		0.85 [0.22, 3.24], 0.8159		0.76 [0.31, 1.88], 0.5579	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5667		-0.01 [-0.14, 0.11], 0.8189		-0.03 [-0.12, 0.06], 0.5696	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4231		0.9943		0.5100	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	5/36 (13.9)	7/80 (8.8)	4/35 (11.4)	13/151 (8.6)	9/71 (12.7)
RR [95%-CI]; p-value	0.61 [0.20, 1.86], 0.3833		0.77 [0.24, 2.45], 0.6525		0.68 [0.30, 1.51], 0.3443	
OR [95%-CI]; p-value	0.57 [0.16, 2.02], 0.3815		0.74 [0.20, 2.72], 0.6532		0.65 [0.26, 1.60], 0.3442	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4129		-0.03 [-0.15, 0.10], 0.6676		-0.04 [-0.13, 0.05], 0.3726	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	4/36 (11.1)	4/64 (6.3)	3/37 (8.1)	13/134 (9.7)	7/73 (9.6)
RR [95%-CI]; p-value	1.16 [0.38, 3.50], 0.7961		0.77 [0.18, 3.26], 0.7234		1.01 [0.42, 2.42], 0.9791	
OR [95%-CI]; p-value	1.18 [0.34, 4.13], 0.7952		0.76 [0.16, 3.58], 0.7232		1.01 [0.39, 2.66], 0.9791	
RD [95%-CI]; p-value	0.02 [-0.11, 0.15], 0.7911		-0.02 [-0.12, 0.09], 0.7314		0.00 [-0.08, 0.09], 0.9791	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.4.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9889		0.5561		0.2832	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	5/80 (6.3)	0/35 (0.0)	7/151 (4.6)	4/71 (5.6)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		4.44 [0.25, 79.06], 0.3106		0.82 [0.25, 2.72], 0.7493	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		4.67 [0.25, 87.80], 0.2596		0.81 [0.23, 2.88], 0.7493	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.05 [-0.02, 0.11], 0.1486		-0.01 [-0.07, 0.05], 0.7571	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	8/36 (22.2)	1/64 (1.6)	0/37 (0.0)	5/134 (3.7)	8/73 (11.0)
RR [95%-CI]; p-value	0.26 [0.08, 0.80], 0.0186		1.17 [0.04, 34.10], 0.9265		0.34 [0.12, 1.00], 0.0506	
OR [95%-CI]; p-value	0.21 [0.06, 0.76], 0.0111		1.17 [0.04, 35.87], 0.9264		0.31 [0.10, 1.00], 0.0406	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0270		0.00 [-0.05, 0.05], 0.9249		-0.07 [-0.15, 0.01], 0.0712	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_4_m_pt_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.4.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4599		0.6195		0.6854	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	6/36 (16.7)	4/80 (5.0)	1/35 (2.9)	7/151 (4.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.25 [0.07, 0.96], 0.0426		1.75 [0.20, 15.10], 0.6108		0.47 [0.17, 1.29], 0.1427	
OR [95%-CI]; p-value	0.22 [0.05, 0.94], 0.0285		1.79 [0.19, 16.61], 0.6041		0.44 [0.15, 1.32], 0.1354	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0615		0.02 [-0.05, 0.09], 0.5650		-0.05 [-0.13, 0.02], 0.1838	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	4/36 (11.1)	3/64 (4.7)	2/37 (5.4)	7/134 (5.2)	6/73 (8.2)
RR [95%-CI]; p-value	0.51 [0.14, 1.94], 0.3258		0.87 [0.15, 4.95], 0.8727		0.64 [0.22, 1.82], 0.3987	
OR [95%-CI]; p-value	0.48 [0.11, 2.06], 0.3192		0.86 [0.14, 5.40], 0.8727		0.62 [0.20, 1.91], 0.3960	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3625		-0.01 [-0.10, 0.08], 0.8749		-0.03 [-0.10, 0.04], 0.4239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_4_m_pt_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.4.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.9895		0.3682		0.4560	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	4/71 (5.6)	2/36 (5.6)	4/80 (5.0)	4/35 (11.4)	8/151 (5.3)	6/71 (8.5)
RR [95%-CI]; p-value	1.01 [0.19, 5.28], 0.9867		0.44 [0.12, 1.65], 0.2224		0.63 [0.23, 1.74], 0.3697	
OR [95%-CI]; p-value	1.01 [0.18, 5.82], 0.9867		0.41 [0.10, 1.73], 0.2125		0.61 [0.20, 1.82], 0.3674	
RD [95%-CI]; p-value	0.00 [-0.09, 0.09], 0.9867		-0.06 [-0.18, 0.05], 0.2762		-0.03 [-0.11, 0.04], 0.4031	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	3/36 (8.3)	4/64 (6.3)	2/37 (5.4)	10/134 (7.5)	5/73 (6.8)
RR [95%-CI]; p-value	1.03 [0.27, 3.87], 0.9668		1.16 [0.22, 6.01], 0.8629		1.09 [0.39, 3.07], 0.8710	
OR [95%-CI]; p-value	1.03 [0.24, 4.39], 0.9668		1.17 [0.20, 6.70], 0.8626		1.10 [0.36, 3.34], 0.8708	
RD [95%-CI]; p-value	0.00 [-0.11, 0.11], 0.9666		0.01 [-0.09, 0.10], 0.8601		0.01 [-0.07, 0.08], 0.8693	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_4_m_pt_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.0961		0.6882		0.2988	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	2/36 (5.6)	4/80 (5.0)	2/35 (5.7)	7/151 (4.6)	4/71 (5.6)
RR [95%-CI]; p-value	0.76 [0.13, 4.35], 0.7584		0.88 [0.17, 4.56], 0.8740		0.82 [0.25, 2.72], 0.7493	
OR [95%-CI]; p-value	0.75 [0.12, 4.70], 0.7581		0.87 [0.15, 4.98], 0.8741		0.81 [0.23, 2.88], 0.7493	
RD [95%-CI]; p-value	-0.01 [-0.10, 0.07], 0.7677		-0.01 [-0.10, 0.08], 0.8771		-0.01 [-0.07, 0.05], 0.7571	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	0/36 (0.0)	5/64 (7.8)	5/37 (13.5)	17/134 (12.7)	5/73 (6.8)
RR [95%-CI]; p-value	12.51 [0.76, 205.90], 0.0770		0.58 [0.18, 1.87], 0.3593		1.85 [0.71, 4.82], 0.2061	
OR [95%-CI]; p-value	14.90 [0.85, 259.95], 0.0164		0.54 [0.15, 2.01], 0.3554		1.98 [0.70, 5.60], 0.1929	
RD [95%-CI]; p-value	0.16 [0.06, 0.25], 0.0013		-0.06 [-0.19, 0.07], 0.3837		0.06 [-0.02, 0.14], 0.1569	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5785		0.4886		0.2507	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	0/71 (0.0)	0/36 (0.0)	0/80 (0.0)	1/35 (2.9)	0/151 (0.0)	1/71 (1.4)
RR [95%-CI]; p-value	NA		0.22 [0.01, 6.33], 0.3750		0.23 [0.01, 6.90], 0.4005	
OR [95%-CI]; p-value	NA		0.21 [0.01, 6.49], 0.3293		0.23 [0.01, 6.99], 0.3595	
RD [95%-CI]; p-value	NA		-0.02 [-0.08, 0.04], 0.4483		-0.01 [-0.04, 0.02], 0.4644	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	1/64 (1.6)	0/37 (0.0)	3/134 (2.2)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		1.17 [0.04, 34.10], 0.9265		3.29 [0.17, 64.82], 0.4334	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		1.17 [0.04, 35.87], 0.9264		3.34 [0.17, 67.67], 0.4044	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.00 [-0.05, 0.05], 0.9249		0.02 [-0.02, 0.05], 0.3293	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.1209		0.2952		0.6949	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	2/36 (5.6)	4/80 (5.0)	1/35 (2.9)	7/151 (4.6)	3/71 (4.2)
RR [95%-CI]; p-value	0.76 [0.13, 4.35], 0.7584		1.75 [0.20, 15.10], 0.6108		1.10 [0.29, 4.12], 0.8908	
OR [95%-CI]; p-value	0.75 [0.12, 4.70], 0.7581		1.79 [0.19, 16.61], 0.6041		1.10 [0.28, 4.39], 0.8906	
RD [95%-CI]; p-value	-0.01 [-0.10, 0.07], 0.7677		0.02 [-0.05, 0.09], 0.5650		0.00 [-0.05, 0.06], 0.8889	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	0/36 (0.0)	4/64 (6.3)	5/37 (13.5)	14/134 (10.4)	5/73 (6.8)
RR [95%-CI]; p-value	10.43 [0.63, 173.55], 0.1022		0.46 [0.13, 1.62], 0.2270		1.53 [0.57, 4.07], 0.3987	
OR [95%-CI]; p-value	12.00 [0.68, 211.68], 0.0338		0.43 [0.11, 1.70], 0.2170		1.59 [0.55, 4.60], 0.3916	
RD [95%-CI]; p-value	0.13 [0.04, 0.22], 0.0050		-0.07 [-0.20, 0.05], 0.2551		0.04 [-0.04, 0.11], 0.3641	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.3892		0.8584		0.4953	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	1/36 (2.8)	2/80 (2.5)	0/35 (0.0)	4/151 (2.6)	1/71 (1.4)
RR [95%-CI]; p-value	1.01 [0.10, 10.81], 0.9908		1.78 [0.08, 38.38], 0.7144		1.88 [0.21, 16.52], 0.5689	
OR [95%-CI]; p-value	1.01 [0.09, 11.58], 0.9908		1.79 [0.08, 40.83], 0.7099		1.90 [0.21, 17.36], 0.5612	
RD [95%-CI]; p-value	0.00 [-0.07, 0.07], 0.9907		0.01 [-0.04, 0.06], 0.6790		0.01 [-0.03, 0.05], 0.5169	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	0/36 (0.0)	1/64 (1.6)	0/37 (0.0)	6/134 (4.5)	0/73 (0.0)
RR [95%-CI]; p-value	5.21 [0.29, 92.84], 0.2610		1.17 [0.04, 34.10], 0.9265		6.58 [0.37, 116.20], 0.1983	
OR [95%-CI]; p-value	5.54 [0.29, 104.29], 0.2014		1.17 [0.04, 35.87], 0.9264		6.84 [0.38, 124.29], 0.1331	
RD [95%-CI]; p-value	0.06 [-0.01, 0.13], 0.1118		0.00 [-0.05, 0.05], 0.9249		0.04 [-0.00, 0.08], 0.0611	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.1798		0.6142		0.1767	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	7/36 (19.4)	8/80 (10.0)	4/35 (11.4)	14/151 (9.3)	11/71 (15.5)
RR [95%-CI]; p-value	0.43 [0.16, 1.20], 0.1072		0.88 [0.28, 2.72], 0.8173		0.60 [0.29, 1.25], 0.1725	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1000		0.86 [0.24, 3.07], 0.8176		0.56 [0.24, 1.30], 0.1714	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.03], 0.1361		-0.01 [-0.14, 0.11], 0.8217		-0.06 [-0.16, 0.03], 0.2042	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	2/36 (5.6)	5/64 (7.8)	2/37 (5.4)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	1.54 [0.33, 7.26], 0.5832		1.45 [0.30, 7.08], 0.6496		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	1.59 [0.31, 8.33], 0.5777		1.48 [0.27, 8.06], 0.6463		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	0.03 [-0.07, 0.13], 0.5524		0.02 [-0.07, 0.12], 0.6307		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5785		0.6186		0.4238	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	0/71 (0.0)	0/36 (0.0)	2/80 (2.5)	1/35 (2.9)	2/151 (1.3)	1/71 (1.4)
RR [95%-CI]; p-value	NA		0.88 [0.08, 9.34], 0.9120		0.94 [0.09, 10.20], 0.9597	
OR [95%-CI]; p-value	NA		0.87 [0.08, 9.94], 0.9120		0.94 [0.08, 10.54], 0.9597	
RD [95%-CI]; p-value	NA		-0.00 [-0.07, 0.06], 0.9142		-0.00 [-0.03, 0.03], 0.9601	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	2/64 (3.1)	0/37 (0.0)	4/134 (3.0)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		2.34 [0.11, 50.62], 0.5869		4.39 [0.24, 81.86], 0.3219	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		2.39 [0.10, 54.36], 0.5741		4.49 [0.23, 86.16], 0.2756	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.02 [-0.04, 0.07], 0.5325		0.02 [-0.01, 0.06], 0.1891	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
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N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.3831		0.9072		0.4536	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	7/36 (19.4)	7/80 (8.8)	4/35 (11.4)	13/151 (8.6)	11/71 (15.5)
RR [95%-CI]; p-value	0.43 [0.16, 1.20], 0.1072		0.77 [0.24, 2.45], 0.6525		0.56 [0.26, 1.18], 0.1256	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1000		0.74 [0.20, 2.72], 0.6532		0.51 [0.22, 1.21], 0.1234	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.03], 0.1361		-0.03 [-0.15, 0.10], 0.6676		-0.07 [-0.16, 0.03], 0.1569	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	2/36 (5.6)	3/64 (4.7)	2/37 (5.4)	7/134 (5.2)	4/73 (5.5)
RR [95%-CI]; p-value	1.03 [0.20, 5.35], 0.9733		0.87 [0.15, 4.95], 0.8727		0.95 [0.29, 3.15], 0.9376	
OR [95%-CI]; p-value	1.03 [0.18, 5.91], 0.9733		0.86 [0.14, 5.40], 0.8727		0.95 [0.27, 3.36], 0.9376	
RD [95%-CI]; p-value	0.00 [-0.09, 0.09], 0.9732		-0.01 [-0.10, 0.08], 0.8749		-0.00 [-0.07, 0.06], 0.9380	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8575		0.7646		0.8100	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	0/36 (0.0)	3/80 (3.8)	1/35 (2.9)	6/151 (4.0)	1/71 (1.4)
RR [95%-CI]; p-value	3.08 [0.16, 59.95], 0.4569		1.31 [0.14, 12.18], 0.8109		2.82 [0.35, 23.00], 0.3326	
OR [95%-CI]; p-value	3.18 [0.15, 65.16], 0.4295		1.32 [0.13, 13.20], 0.8100		2.90 [0.34, 24.52], 0.3077	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3517		0.01 [-0.06, 0.08], 0.8002		0.03 [-0.02, 0.07], 0.2257	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	2/64 (3.1)	0/37 (0.0)	4/134 (3.0)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		2.34 [0.11, 50.62], 0.5869		4.39 [0.24, 81.86], 0.3219	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		2.39 [0.10, 54.36], 0.5741		4.49 [0.23, 86.16], 0.2756	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.02 [-0.04, 0.07], 0.5325		0.02 [-0.01, 0.06], 0.1891	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.6.s5
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.7064		0.3421		0.2831	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	12/71 (16.9)	8/36 (22.2)	19/80 (23.8)	4/35 (11.4)	31/151 (20.5)	12/71 (16.9)
RR [95%-CI]; p-value	0.76 [0.34, 1.69], 0.5023		2.08 [0.76, 5.66], 0.1526		1.21 [0.66, 2.22], 0.5278	
OR [95%-CI]; p-value	0.71 [0.26, 1.94], 0.5047		2.41 [0.76, 7.71], 0.1285		1.27 [0.61, 2.65], 0.5234	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5181		0.12 [-0.02, 0.26], 0.0862		0.04 [-0.07, 0.14], 0.5118	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	10/36 (27.8)	9/64 (14.1)	5/37 (13.5)	21/134 (15.7)	15/73 (20.5)
RR [95%-CI]; p-value	0.62 [0.30, 1.29], 0.1991		1.04 [0.38, 2.87], 0.9387		0.76 [0.42, 1.39], 0.3747	
OR [95%-CI]; p-value	0.54 [0.21, 1.40], 0.2010		1.05 [0.32, 3.40], 0.9387		0.72 [0.34, 1.50], 0.3765	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.2226		0.01 [-0.13, 0.14], 0.9384		-0.05 [-0.16, 0.06], 0.3904	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_6_m_pt_adr_ckd.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.6730		0.3370		0.8882	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	30/43 (69.8)	20/26 (76.9)	32/53 (60.4)	9/20 (45.0)	62/96 (64.6)	29/46 (63.0)
RR [95%-CI]; p-value	0.91 [0.68, 1.21], 0.5066		1.34 [0.79, 2.28], 0.2782		1.02 [0.78, 1.34], 0.8590	
OR [95%-CI]; p-value	0.69 [0.23, 2.12], 0.5191		1.86 [0.66, 5.26], 0.2376		1.07 [0.51, 2.22], 0.8579	
RD [95%-CI]; p-value	-0.07 [-0.28, 0.14], 0.5089		0.15 [-0.10, 0.41], 0.2367		0.02 [-0.15, 0.18], 0.8584	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	37/50 (74.0)	16/22 (72.7)	27/44 (61.4)	20/28 (71.4)	64/94 (68.1)	36/50 (72.0)
RR [95%-CI]; p-value	1.02 [0.75, 1.38], 0.9110		0.86 [0.62, 1.20], 0.3691		0.95 [0.76, 1.18], 0.6207	
OR [95%-CI]; p-value	1.07 [0.34, 3.31], 0.9101		0.64 [0.23, 1.76], 0.3818		0.83 [0.39, 1.76], 0.6273	
RD [95%-CI]; p-value	0.01 [-0.21, 0.24], 0.9107		-0.10 [-0.32, 0.12], 0.3714		-0.04 [-0.20, 0.12], 0.6231	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	34/48 (70.8)	20/24 (83.3)	32/47 (68.1)	15/24 (62.5)	66/95 (69.5)	35/48 (72.9)
RR [95%-CI]; p-value	0.85 [0.66, 1.10], 0.2114		1.09 [0.76, 1.57], 0.6472		0.95 [0.77, 1.18], 0.6636	
OR [95%-CI]; p-value	0.49 [0.14, 1.68], 0.2482		1.28 [0.46, 3.58], 0.6379		0.85 [0.39, 1.83], 0.6695	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.07], 0.2134		0.06 [-0.18, 0.29], 0.6415		-0.03 [-0.19, 0.12], 0.6656	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.8478		0.4543		0.3169	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	3/26 (11.5)	3/53 (5.7)	1/20 (5.0)	6/96 (6.3)	4/46 (8.7)
RR [95%-CI]; p-value	0.60 [0.13, 2.78], 0.5177		1.13 [0.12, 10.26], 0.9122		0.72 [0.21, 2.42], 0.5943	
OR [95%-CI]; p-value	0.58 [0.11, 3.09], 0.5146		1.14 [0.11, 11.65], 0.9120		0.70 [0.19, 2.61], 0.5940	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.10], 0.5361		0.01 [-0.11, 0.12], 0.9096		-0.02 [-0.12, 0.07], 0.6129	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	7/50 (14.0)	3/22 (13.6)	8/44 (18.2)	0/28 (0.0)	15/94 (16.0)	3/50 (6.0)
RR [95%-CI]; p-value	1.03 [0.29, 3.61], 0.9672		10.36 [0.62, 173.52], 0.1039		2.66 [0.81, 8.75], 0.1075	
OR [95%-CI]; p-value	1.03 [0.24, 4.42], 0.9672		12.44 [0.69, 226.05], 0.0337		2.97 [0.82, 10.82], 0.0854	
RD [95%-CI]; p-value	0.00 [-0.17, 0.18], 0.9671		0.16 [0.04, 0.29], 0.0093		0.10 [0.00, 0.20], 0.0488	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	5/24 (20.8)	8/47 (17.0)	1/24 (4.2)	15/95 (15.8)	6/48 (12.5)
RR [95%-CI]; p-value	0.70 [0.25, 1.98], 0.5006		4.09 [0.54, 30.79], 0.1721		1.26 [0.52, 3.05], 0.6032	
OR [95%-CI]; p-value	0.65 [0.18, 2.31], 0.5023		4.72 [0.55, 40.17], 0.1236		1.31 [0.47, 3.63], 0.5997	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5206		0.13 [-0.01, 0.26], 0.0599		0.03 [-0.09, 0.15], 0.5876	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.4972		0.4441		0.2234	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	3/26 (11.5)	2/53 (3.8)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.81 [0.20, 3.32], 0.7655		0.38 [0.06, 2.50], 0.3125		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.79 [0.16, 3.83], 0.7656		0.35 [0.05, 2.69], 0.2972		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.13], 0.7707		-0.06 [-0.20, 0.08], 0.3872		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	0/22 (0.0)	5/44 (11.4)	2/28 (7.1)	11/94 (11.7)	2/50 (4.0)
RR [95%-CI]; p-value	5.40 [0.31, 92.59], 0.2448		1.59 [0.33, 7.65], 0.5621		2.93 [0.67, 12.69], 0.1515	
OR [95%-CI]; p-value	6.00 [0.32, 112.37], 0.1776		1.67 [0.30, 9.25], 0.5556		3.18 [0.68, 14.96], 0.1247	
RD [95%-CI]; p-value	0.10 [-0.01, 0.21], 0.0780		0.04 [-0.09, 0.18], 0.5363		0.08 [-0.01, 0.16], 0.0747	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	3/24 (12.5)	3/47 (6.4)	3/24 (12.5)	11/95 (11.6)	6/48 (12.5)
RR [95%-CI]; p-value	1.33 [0.39, 4.58], 0.6475		0.51 [0.11, 2.34], 0.3870		0.93 [0.36, 2.35], 0.8722	
OR [95%-CI]; p-value	1.40 [0.34, 5.84], 0.6432		0.48 [0.09, 2.57], 0.3807		0.92 [0.32, 2.65], 0.8723	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6293		-0.06 [-0.21, 0.09], 0.4230		-0.01 [-0.12, 0.10], 0.8737	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.4906		0.3467		0.5802	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	6/43 (14.0)	5/26 (19.2)	6/53 (11.3)	1/20 (5.0)	12/96 (12.5)	6/46 (13.0)
RR [95%-CI]; p-value	0.73 [0.25, 2.14], 0.5613		2.26 [0.29, 17.65], 0.4354		0.96 [0.38, 2.39], 0.9273	
OR [95%-CI]; p-value	0.68 [0.19, 2.50], 0.5617		2.43 [0.27, 21.52], 0.4133		0.95 [0.33, 2.72], 0.9274	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.13], 0.5730		0.06 [-0.06, 0.19], 0.3334		-0.01 [-0.12, 0.11], 0.9279	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	12/50 (24.0)	3/22 (13.6)	9/44 (20.5)	4/28 (14.3)	21/94 (22.3)	7/50 (14.0)
RR [95%-CI]; p-value	1.76 [0.55, 5.62], 0.3401		1.43 [0.49, 4.21], 0.5141		1.60 [0.73, 3.49], 0.2424	
OR [95%-CI]; p-value	2.00 [0.50, 7.95], 0.3185		1.54 [0.43, 5.59], 0.5071		1.77 [0.69, 4.50], 0.2286	
RD [95%-CI]; p-value	0.10 [-0.08, 0.29], 0.2747		0.06 [-0.11, 0.24], 0.4923		0.08 [-0.04, 0.21], 0.2010	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	12/48 (25.0)	4/24 (16.7)	7/47 (14.9)	6/24 (25.0)	19/95 (20.0)	10/48 (20.8)
RR [95%-CI]; p-value	1.50 [0.54, 4.16], 0.4359		0.60 [0.23, 1.58], 0.2969		0.96 [0.49, 1.90], 0.9067	
OR [95%-CI]; p-value	1.67 [0.47, 5.86], 0.4227		0.53 [0.15, 1.79], 0.2976		0.95 [0.40, 2.24], 0.9068	
RD [95%-CI]; p-value	0.08 [-0.11, 0.28], 0.3973		-0.10 [-0.30, 0.10], 0.3242		-0.01 [-0.15, 0.13], 0.9073	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9106		0.2898		0.3848	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	2/26 (7.7)	3/53 (5.7)	2/20 (10.0)	8/96 (8.3)	4/46 (8.7)
RR [95%-CI]; p-value	1.51 [0.32, 7.24], 0.6050		0.57 [0.10, 3.14], 0.5151		0.96 [0.30, 3.02], 0.9421	
OR [95%-CI]; p-value	1.58 [0.28, 8.80], 0.5998		0.54 [0.08, 3.50], 0.5127		0.95 [0.27, 3.35], 0.9421	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5823		-0.04 [-0.19, 0.10], 0.5587		-0.00 [-0.10, 0.09], 0.9425	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	0/22 (0.0)	6/44 (13.6)	1/28 (3.6)	9/94 (9.6)	1/50 (2.0)
RR [95%-CI]; p-value	2.70 [0.14, 51.70], 0.5096		3.82 [0.49, 30.06], 0.2031		4.79 [0.62, 36.72], 0.1319	
OR [95%-CI]; p-value	2.81 [0.13, 58.50], 0.4875		4.26 [0.48, 37.48], 0.1599		5.19 [0.64, 42.19], 0.0887	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4090		0.10 [-0.02, 0.22], 0.1073		0.08 [0.00, 0.15], 0.0366	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	3/24 (12.5)	6/47 (12.8)	1/24 (4.2)	14/95 (14.7)	4/48 (8.3)
RR [95%-CI]; p-value	1.33 [0.39, 4.58], 0.6475		3.06 [0.39, 24.02], 0.2865		1.77 [0.62, 5.08], 0.2898	
OR [95%-CI]; p-value	1.40 [0.34, 5.84], 0.6432		3.37 [0.38, 29.71], 0.2502		1.90 [0.59, 6.13], 0.2757	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6293		0.09 [-0.04, 0.21], 0.1757		0.06 [-0.04, 0.17], 0.2355	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.6813		0.1695		0.6155	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	0/26 (0.0)	0/53 (0.0)	2/20 (10.0)	3/96 (3.1)	2/46 (4.3)
RR [95%-CI]; p-value	3.70 [0.19, 70.97], 0.3857		0.09 [0.00, 1.99], 0.1285		0.72 [0.12, 4.15], 0.7122	
OR [95%-CI]; p-value	3.90 [0.19, 81.07], 0.3460		0.08 [0.00, 1.97], 0.0564		0.71 [0.11, 4.40], 0.7114	
RD [95%-CI]; p-value	0.05 [-0.04, 0.14], 0.2787		-0.09 [-0.22, 0.04], 0.1848		-0.01 [-0.08, 0.06], 0.7262	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	3/44 (6.8)	1/28 (3.6)	3/94 (3.2)	1/50 (2.0)
RR [95%-CI]; p-value	0.45 [0.01, 21.76], 0.6836		1.91 [0.21, 17.46], 0.5669		1.60 [0.17, 14.94], 0.6822	
OR [95%-CI]; p-value	0.44 [0.01, 22.89], 0.6758		1.98 [0.20, 20.00], 0.5577		1.62 [0.16, 15.95], 0.6787	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.7175		0.03 [-0.07, 0.13], 0.5301		0.01 [-0.04, 0.06], 0.6572	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	2/24 (8.3)	4/47 (8.5)	0/24 (0.0)	9/95 (9.5)	2/48 (4.2)
RR [95%-CI]; p-value	1.25 [0.26, 5.98], 0.7799		4.17 [0.23, 75.72], 0.3343		2.27 [0.51, 10.11], 0.2807	
OR [95%-CI]; p-value	1.28 [0.23, 7.13], 0.7785		4.47 [0.23, 88.09], 0.2850		2.41 [0.50, 11.61], 0.2607	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7711		0.06 [-0.03, 0.16], 0.1932		0.05 [-0.03, 0.13], 0.2026	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.9103		0.5562		0.5854	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	1/26 (3.8)	0/53 (0.0)	1/20 (5.0)	2/96 (2.1)	2/46 (4.3)
RR [95%-CI]; p-value	1.21 [0.12, 12.69], 0.8741		0.19 [0.01, 5.36], 0.3273		0.48 [0.07, 3.30], 0.4546	
OR [95%-CI]; p-value	1.22 [0.11, 14.15], 0.8738		0.18 [0.01, 5.56], 0.2726		0.47 [0.06, 3.43], 0.4453	
RD [95%-CI]; p-value	0.01 [-0.09, 0.11], 0.8709		-0.04 [-0.14, 0.06], 0.4206		-0.02 [-0.09, 0.04], 0.4980	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	1/44 (2.3)	0/28 (0.0)	1/94 (1.1)	0/50 (0.0)
RR [95%-CI]; p-value	0.45 [0.01, 21.76], 0.6836		1.30 [0.04, 37.37], 0.8800		1.07 [0.04, 31.48], 0.9668	
OR [95%-CI]; p-value	0.44 [0.01, 22.89], 0.6758		1.30 [0.04, 40.13], 0.8796		1.08 [0.04, 32.61], 0.9667	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.7175		0.01 [-0.06, 0.07], 0.8763		0.00 [-0.03, 0.04], 0.9664	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	1/48 (2.1)	0/24 (0.0)	2/47 (4.3)	0/24 (0.0)	3/95 (3.2)	0/48 (0.0)
RR [95%-CI]; p-value	1.02 [0.04, 29.38], 0.9904		2.09 [0.10, 44.48], 0.6379		3.06 [0.16, 59.94], 0.4606	
OR [95%-CI]; p-value	1.02 [0.03, 31.54], 0.9904		2.13 [0.09, 49.21], 0.6285		3.13 [0.15, 63.77], 0.4346	
RD [95%-CI]; p-value	0.00 [-0.07, 0.07], 0.9904		0.02 [-0.06, 0.10], 0.5893		0.02 [-0.02, 0.07], 0.3566	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.9647		0.3308		0.8165	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	26/43 (60.5)	19/26 (73.1)	27/53 (50.9)	7/20 (35.0)	53/96 (55.2)	26/46 (56.5)
RR [95%-CI]; p-value	0.83 [0.59, 1.16], 0.2690		1.46 [0.76, 2.80], 0.2599		0.98 [0.72, 1.33], 0.8822	
OR [95%-CI]; p-value	0.56 [0.20, 1.63], 0.2865		1.93 [0.66, 5.59], 0.2232		0.95 [0.47, 1.93], 0.8828	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.10], 0.2710		0.16 [-0.09, 0.41], 0.2088		-0.01 [-0.19, 0.16], 0.8827	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	28/50 (56.0)	14/22 (63.6)	20/44 (45.5)	16/28 (57.1)	48/94 (51.1)	30/50 (60.0)
RR [95%-CI]; p-value	0.88 [0.59, 1.31], 0.5313		0.80 [0.50, 1.25], 0.3250		0.85 [0.63, 1.15], 0.2931	
OR [95%-CI]; p-value	0.73 [0.26, 2.04], 0.5449		0.63 [0.24, 1.62], 0.3336		0.70 [0.35, 1.39], 0.3055	
RD [95%-CI]; p-value	-0.08 [-0.32, 0.17], 0.5389		-0.12 [-0.35, 0.12], 0.3297		-0.09 [-0.26, 0.08], 0.3008	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	28/48 (58.3)	17/24 (70.8)	23/47 (48.9)	12/24 (50.0)	51/95 (53.7)	29/48 (60.4)
RR [95%-CI]; p-value	0.82 [0.58, 1.17], 0.2780		0.98 [0.60, 1.61], 0.9322		0.89 [0.66, 1.19], 0.4333	
OR [95%-CI]; p-value	0.58 [0.20, 1.65], 0.3017		0.96 [0.36, 2.56], 0.9324		0.76 [0.38, 1.54], 0.4438	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.10], 0.2850		-0.01 [-0.26, 0.24], 0.9324		-0.07 [-0.24, 0.10], 0.4399	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.6864		0.5150		0.3321	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	13/43 (30.2)	10/26 (38.5)	14/53 (26.4)	4/20 (20.0)	27/96 (28.1)	14/46 (30.4)
RR [95%-CI]; p-value	0.79 [0.40, 1.53], 0.4782		1.32 [0.49, 3.54], 0.5799		0.92 [0.54, 1.59], 0.7751	
OR [95%-CI]; p-value	0.69 [0.25, 1.93], 0.4823		1.44 [0.41, 5.03], 0.5706		0.89 [0.41, 1.93], 0.7762	
RD [95%-CI]; p-value	-0.08 [-0.31, 0.15], 0.4869		0.06 [-0.15, 0.28], 0.5526		-0.02 [-0.18, 0.14], 0.7779	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	20/50 (40.0)	8/22 (36.4)	16/44 (36.4)	5/28 (17.9)	36/94 (38.3)	13/50 (26.0)
RR [95%-CI]; p-value	1.10 [0.57, 2.10], 0.7734		2.04 [0.84, 4.94], 0.1154		1.47 [0.86, 2.51], 0.1547	
OR [95%-CI]; p-value	1.17 [0.41, 3.29], 0.7706		2.63 [0.84, 8.27], 0.0921		1.77 [0.83, 3.76], 0.1381	
RD [95%-CI]; p-value	0.04 [-0.21, 0.28], 0.7689		0.19 [-0.02, 0.39], 0.0709		0.12 [-0.03, 0.28], 0.1231	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	17/48 (35.4)	11/24 (45.8)	19/47 (40.4)	9/24 (37.5)	36/95 (37.9)	20/48 (41.7)
RR [95%-CI]; p-value	0.77 [0.43, 1.38], 0.3827		1.08 [0.58, 2.01], 0.8130		0.91 [0.60, 1.39], 0.6596	
OR [95%-CI]; p-value	0.65 [0.24, 1.76], 0.3927		1.13 [0.41, 3.11], 0.8114		0.85 [0.42, 1.73], 0.6626	
RD [95%-CI]; p-value	-0.10 [-0.35, 0.14], 0.3968		0.03 [-0.21, 0.27], 0.8105		-0.04 [-0.21, 0.13], 0.6640	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.4972		0.4441		0.2234	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	3/26 (11.5)	2/53 (3.8)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.81 [0.20, 3.32], 0.7655		0.38 [0.06, 2.50], 0.3125		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.79 [0.16, 3.83], 0.7656		0.35 [0.05, 2.69], 0.2972		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.13], 0.7707		-0.06 [-0.20, 0.08], 0.3872		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	0/22 (0.0)	5/44 (11.4)	2/28 (7.1)	11/94 (11.7)	2/50 (4.0)
RR [95%-CI]; p-value	5.40 [0.31, 92.59], 0.2448		1.59 [0.33, 7.65], 0.5621		2.93 [0.67, 12.69], 0.1515	
OR [95%-CI]; p-value	6.00 [0.32, 112.37], 0.1776		1.67 [0.30, 9.25], 0.5556		3.18 [0.68, 14.96], 0.1247	
RD [95%-CI]; p-value	0.10 [-0.01, 0.21], 0.0780		0.04 [-0.09, 0.18], 0.5363		0.08 [-0.01, 0.16], 0.0747	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	3/24 (12.5)	3/47 (6.4)	3/24 (12.5)	11/95 (11.6)	6/48 (12.5)
RR [95%-CI]; p-value	1.33 [0.39, 4.58], 0.6475		0.51 [0.11, 2.34], 0.3870		0.93 [0.36, 2.35], 0.8722	
OR [95%-CI]; p-value	1.40 [0.34, 5.84], 0.6432		0.48 [0.09, 2.57], 0.3807		0.92 [0.32, 2.65], 0.8723	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6293		-0.06 [-0.21, 0.09], 0.4230		-0.01 [-0.12, 0.10], 0.8737	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7392		0.6985		0.6210	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	3/26 (11.5)	4/53 (7.5)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.40 [0.07, 2.25], 0.3010		0.75 [0.15, 3.80], 0.7331		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.37 [0.06, 2.40], 0.2849		0.73 [0.12, 4.36], 0.7336		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3280		-0.02 [-0.17, 0.12], 0.7477		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	4/22 (18.2)	3/44 (6.8)	1/28 (3.6)	8/94 (8.5)	5/50 (10.0)
RR [95%-CI]; p-value	0.55 [0.16, 1.85], 0.3350		1.91 [0.21, 17.46], 0.5669		0.85 [0.29, 2.46], 0.7663	
OR [95%-CI]; p-value	0.50 [0.12, 2.08], 0.3336		1.98 [0.20, 20.00], 0.5577		0.84 [0.26, 2.71], 0.7665	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3766		0.03 [-0.07, 0.13], 0.5301		-0.01 [-0.12, 0.09], 0.7714	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	2/24 (8.3)	4/47 (8.5)	1/24 (4.2)	8/95 (8.4)	3/48 (6.3)
RR [95%-CI]; p-value	1.00 [0.20, 5.08], 1.0000		2.04 [0.24, 17.28], 0.5121		1.35 [0.37, 4.85], 0.6482	
OR [95%-CI]; p-value	1.00 [0.17, 5.89], 1.0000		2.14 [0.23, 20.28], 0.4986		1.38 [0.35, 5.45], 0.6455	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		0.04 [-0.07, 0.16], 0.4509		0.02 [-0.07, 0.11], 0.6301	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.7018		0.7377		0.7083	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	10/43 (23.3)	8/26 (30.8)	9/53 (17.0)	1/20 (5.0)	19/96 (19.8)	9/46 (19.6)
RR [95%-CI]; p-value	0.76 [0.34, 1.67], 0.4884		3.40 [0.46, 25.12], 0.2311		1.01 [0.50, 2.06], 0.9747	
OR [95%-CI]; p-value	0.68 [0.23, 2.03], 0.4910		3.89 [0.46, 32.86], 0.1842		1.01 [0.42, 2.46], 0.9747	
RD [95%-CI]; p-value	-0.08 [-0.29, 0.14], 0.4989		0.12 [-0.02, 0.26], 0.0913		0.00 [-0.14, 0.14], 0.9746	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	9/50 (18.0)	4/22 (18.2)	6/44 (13.6)	2/28 (7.1)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	0.99 [0.34, 2.87], 0.9853		1.91 [0.41, 8.80], 0.4070		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	0.99 [0.27, 3.63], 0.9853		2.05 [0.38, 10.97], 0.3927		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	-0.00 [-0.19, 0.19], 0.9853		0.06 [-0.07, 0.20], 0.3606		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	8/24 (33.3)	11/47 (23.4)	4/24 (16.7)	20/95 (21.1)	12/48 (25.0)
RR [95%-CI]; p-value	0.56 [0.25, 1.27], 0.1673		1.40 [0.50, 3.95], 0.5196		0.84 [0.45, 1.57], 0.5905	
OR [95%-CI]; p-value	0.46 [0.15, 1.41], 0.1696		1.53 [0.43, 5.43], 0.5106		0.80 [0.35, 1.81], 0.5928	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.07], 0.1909		0.07 [-0.12, 0.26], 0.4917		-0.04 [-0.19, 0.11], 0.5997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.3480		0.4449		0.1769	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	7/26 (26.9)	5/53 (9.4)	3/20 (15.0)	9/96 (9.4)	10/46 (21.7)
RR [95%-CI]; p-value	0.35 [0.11, 1.07], 0.0648		0.63 [0.17, 2.39], 0.4962		0.43 [0.19, 0.99], 0.0468	
OR [95%-CI]; p-value	0.28 [0.07, 1.07], 0.0527		0.59 [0.13, 2.74], 0.4971		0.37 [0.14, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.18 [-0.37, 0.02], 0.0711		-0.06 [-0.23, 0.12], 0.5334		-0.12 [-0.26, 0.01], 0.0678	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	8/50 (16.0)	3/22 (13.6)	7/44 (15.9)	3/28 (10.7)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	1.17 [0.34, 4.01], 0.7987		1.48 [0.42, 5.27], 0.5408		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	1.21 [0.29, 5.06], 0.7973		1.58 [0.37, 6.68], 0.5344		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7921		0.05 [-0.11, 0.21], 0.5180		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	5/24 (20.8)	5/47 (10.6)	5/24 (20.8)	12/95 (12.6)	10/48 (20.8)
RR [95%-CI]; p-value	0.70 [0.25, 1.98], 0.5006		0.51 [0.16, 1.59], 0.2470		0.61 [0.28, 1.30], 0.1993	
OR [95%-CI]; p-value	0.65 [0.18, 2.31], 0.5023		0.45 [0.12, 1.75], 0.2427		0.55 [0.22, 1.38], 0.1993	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5206		-0.10 [-0.29, 0.08], 0.2797		-0.08 [-0.21, 0.05], 0.2264	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2110		0.5244		0.7191	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	6/26 (23.1)	11/53 (20.8)	3/20 (15.0)	22/96 (22.9)	9/46 (19.6)
RR [95%-CI]; p-value	1.11 [0.47, 2.64], 0.8159		1.38 [0.43, 4.45], 0.5859		1.17 [0.59, 2.34], 0.6540	
OR [95%-CI]; p-value	1.15 [0.37, 3.59], 0.8150		1.48 [0.37, 5.99], 0.5775		1.22 [0.51, 2.92], 0.6510	
RD [95%-CI]; p-value	0.03 [-0.18, 0.23], 0.8134		0.06 [-0.13, 0.25], 0.5545		0.03 [-0.11, 0.18], 0.6440	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	17/50 (34.0)	5/22 (22.7)	9/44 (20.5)	8/28 (28.6)	26/94 (27.7)	13/50 (26.0)
RR [95%-CI]; p-value	1.50 [0.63, 3.54], 0.3597		0.72 [0.31, 1.64], 0.4279		1.06 [0.60, 1.88], 0.8317	
OR [95%-CI]; p-value	1.75 [0.55, 5.57], 0.3388		0.64 [0.21, 1.93], 0.4292		1.09 [0.50, 2.37], 0.8311	
RD [95%-CI]; p-value	0.11 [-0.11, 0.33], 0.3128		-0.08 [-0.29, 0.12], 0.4387		0.02 [-0.13, 0.17], 0.8300	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	9/24 (37.5)	13/47 (27.7)	5/24 (20.8)	23/95 (24.2)	14/48 (29.2)
RR [95%-CI]; p-value	0.56 [0.26, 1.18], 0.1273		1.33 [0.54, 3.29], 0.5401		0.83 [0.47, 1.46], 0.5194	
OR [95%-CI]; p-value	0.44 [0.15, 1.29], 0.1304		1.45 [0.45, 4.70], 0.5317		0.78 [0.36, 1.69], 0.5228	
RD [95%-CI]; p-value	-0.17 [-0.39, 0.06], 0.1469		0.07 [-0.14, 0.28], 0.5176		-0.05 [-0.20, 0.11], 0.5302	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.3456		0.5882		0.6032	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	7/96 (7.3)	3/46 (6.5)
RR [95%-CI]; p-value	1.51 [0.32, 7.24], 0.6050		0.75 [0.07, 7.87], 0.8140		1.12 [0.30, 4.13], 0.8670	
OR [95%-CI]; p-value	1.58 [0.28, 8.80], 0.5998		0.75 [0.06, 8.70], 0.8139		1.13 [0.28, 4.57], 0.8667	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5823		-0.01 [-0.12, 0.10], 0.8245		0.01 [-0.08, 0.10], 0.8643	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	3/22 (13.6)	4/44 (9.1)	0/28 (0.0)	9/94 (9.6)	3/50 (6.0)
RR [95%-CI]; p-value	0.73 [0.19, 2.80], 0.6502		5.18 [0.28, 94.36], 0.2665		1.60 [0.45, 5.63], 0.4675	
OR [95%-CI]; p-value	0.70 [0.15, 3.24], 0.6511		5.60 [0.28, 110.18], 0.2060		1.66 [0.43, 6.43], 0.4600	
RD [95%-CI]; p-value	-0.04 [-0.20, 0.13], 0.6672		0.07 [-0.02, 0.17], 0.1409		0.04 [-0.05, 0.12], 0.4297	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	0/24 (0.0)	5/47 (10.6)	2/24 (8.3)	12/95 (12.6)	2/48 (4.2)
RR [95%-CI]; p-value	7.15 [0.42, 120.79], 0.1728		1.28 [0.27, 6.10], 0.7596		3.03 [0.71, 13.00], 0.1355	
OR [95%-CI]; p-value	8.20 [0.45, 150.89], 0.0972		1.31 [0.23, 7.31], 0.7579		3.33 [0.71, 15.51], 0.1077	
RD [95%-CI]; p-value	0.13 [0.01, 0.24], 0.0318		0.02 [-0.12, 0.16], 0.7494		0.08 [-0.00, 0.17], 0.0580	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.4574		0.7323		0.4402	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	4/26 (15.4)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	6/46 (13.0)
RR [95%-CI]; p-value	0.45 [0.11, 1.87], 0.2736		0.94 [0.20, 4.48], 0.9415		0.64 [0.24, 1.73], 0.3791	
OR [95%-CI]; p-value	0.41 [0.08, 2.01], 0.2623		0.94 [0.17, 5.27], 0.9416		0.61 [0.20, 1.86], 0.3783	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2976		-0.01 [-0.16, 0.15], 0.9423		-0.05 [-0.16, 0.06], 0.4095	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	1/22 (4.5)	5/44 (11.4)	2/28 (7.1)	10/94 (10.6)	3/50 (6.0)
RR [95%-CI]; p-value	2.20 [0.27, 17.75], 0.4592		1.59 [0.33, 7.65], 0.5621		1.77 [0.51, 6.15], 0.3668	
OR [95%-CI]; p-value	2.33 [0.26, 21.24], 0.4405		1.67 [0.30, 9.25], 0.5556		1.87 [0.49, 7.11], 0.3551	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3745		0.04 [-0.09, 0.18], 0.5363		0.05 [-0.04, 0.14], 0.3160	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	13/95 (13.7)	8/48 (16.7)
RR [95%-CI]; p-value	0.90 [0.34, 2.39], 0.8326		0.68 [0.17, 2.80], 0.5941		0.82 [0.37, 1.84], 0.6331	
OR [95%-CI]; p-value	0.88 [0.26, 2.98], 0.8332		0.65 [0.13, 3.18], 0.5938		0.79 [0.30, 2.07], 0.6342	
RD [95%-CI]; p-value	-0.02 [-0.22, 0.18], 0.8353		-0.04 [-0.19, 0.11], 0.6128		-0.03 [-0.16, 0.10], 0.6429	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.2418		0.4047		0.4582	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	9/26 (34.6)	8/53 (15.1)	2/20 (10.0)	13/96 (13.5)	11/46 (23.9)
RR [95%-CI]; p-value	0.34 [0.13, 0.89], 0.0289		1.51 [0.35, 6.51], 0.5809		0.57 [0.28, 1.17], 0.1226	
OR [95%-CI]; p-value	0.25 [0.07, 0.85], 0.0214		1.60 [0.31, 8.27], 0.5724		0.50 [0.20, 1.22], 0.1228	
RD [95%-CI]; p-value	-0.23 [-0.44, -0.02], 0.0291		0.05 [-0.11, 0.21], 0.5402		-0.10 [-0.24, 0.04], 0.1494	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	13/50 (26.0)	7/22 (31.8)	7/44 (15.9)	3/28 (10.7)	20/94 (21.3)	10/50 (20.0)
RR [95%-CI]; p-value	0.82 [0.38, 1.76], 0.6072		1.48 [0.42, 5.27], 0.5408		1.06 [0.54, 2.09], 0.8579	
OR [95%-CI]; p-value	0.75 [0.25, 2.26], 0.6116		1.58 [0.37, 6.68], 0.5344		1.08 [0.46, 2.53], 0.8575	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.17], 0.6192		0.05 [-0.11, 0.21], 0.5180		0.01 [-0.13, 0.15], 0.8565	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	5/24 (20.8)	10/47 (21.3)	8/24 (33.3)	20/95 (21.1)	13/48 (27.1)
RR [95%-CI]; p-value	1.00 [0.38, 2.60], 1.0000		0.64 [0.29, 1.41], 0.2648		0.78 [0.42, 1.42], 0.4152	
OR [95%-CI]; p-value	1.00 [0.30, 3.34], 1.0000		0.54 [0.18, 1.62], 0.2693		0.72 [0.32, 1.61], 0.4189	
RD [95%-CI]; p-value	0.00 [-0.20, 0.20], 1.0000		-0.12 [-0.34, 0.10], 0.2870		-0.06 [-0.21, 0.09], 0.4310	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3193		0.1824		0.0755	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	8/26 (30.8)	13/53 (24.5)	3/20 (15.0)	24/96 (25.0)	11/46 (23.9)
RR [95%-CI]; p-value	0.83 [0.39, 1.79], 0.6382		1.64 [0.52, 5.14], 0.4000		1.05 [0.56, 1.95], 0.8884	
OR [95%-CI]; p-value	0.77 [0.26, 2.27], 0.6402		1.84 [0.46, 7.30], 0.3801		1.06 [0.47, 2.41], 0.8881	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.17], 0.6442		0.10 [-0.10, 0.29], 0.3375		0.01 [-0.14, 0.16], 0.8875	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	7/22 (31.8)	4/44 (9.1)	7/28 (25.0)	9/94 (9.6)	14/50 (28.0)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		0.36 [0.12, 1.13], 0.0802		0.34 [0.16, 0.73], 0.0059	
OR [95%-CI]; p-value	0.24 [0.07, 0.86], 0.0221		0.30 [0.08, 1.14], 0.0674		0.27 [0.11, 0.69], 0.0041	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0433		-0.16 [-0.34, 0.02], 0.0858		-0.18 [-0.32, -0.05], 0.0088	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	8/24 (33.3)	5/47 (10.6)	4/24 (16.7)	13/95 (13.7)	12/48 (25.0)
RR [95%-CI]; p-value	0.50 [0.21, 1.17], 0.1094		0.64 [0.19, 2.16], 0.4705		0.55 [0.27, 1.11], 0.0932	
OR [95%-CI]; p-value	0.40 [0.13, 1.25], 0.1088		0.60 [0.14, 2.46], 0.4702		0.48 [0.20, 1.14], 0.0925	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.05], 0.1306		-0.06 [-0.23, 0.11], 0.4951		-0.11 [-0.25, 0.03], 0.1148	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.6254		0.6749		0.5805	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	4/26 (15.4)	5/53 (9.4)	0/20 (0.0)	10/96 (10.4)	4/46 (8.7)
RR [95%-CI]; p-value	0.76 [0.22, 2.56], 0.6532		3.87 [0.22, 67.68], 0.3543		1.20 [0.40, 3.62], 0.7487	
OR [95%-CI]; p-value	0.72 [0.18, 2.98], 0.6534		4.17 [0.22, 79.89], 0.3067		1.22 [0.36, 4.12], 0.7475	
RD [95%-CI]; p-value	-0.04 [-0.21, 0.13], 0.6622		0.07 [-0.03, 0.17], 0.1841		0.02 [-0.08, 0.12], 0.7404	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	6/22 (27.3)	6/44 (13.6)	4/28 (14.3)	11/94 (11.7)	10/50 (20.0)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0675		0.95 [0.30, 3.09], 0.9380		0.59 [0.27, 1.28], 0.1806	
OR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0606		0.95 [0.24, 3.71], 0.9381		0.53 [0.21, 1.35], 0.1792	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.03], 0.0967		-0.01 [-0.17, 0.16], 0.9384		-0.08 [-0.21, 0.05], 0.2057	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	3/24 (12.5)	9/47 (19.1)	4/24 (16.7)	11/95 (11.6)	7/48 (14.6)
RR [95%-CI]; p-value	0.33 [0.06, 1.86], 0.2108		1.15 [0.39, 3.35], 0.7993		0.79 [0.33, 1.92], 0.6081	
OR [95%-CI]; p-value	0.30 [0.05, 1.96], 0.1898		1.18 [0.32, 4.33], 0.7981		0.77 [0.28, 2.12], 0.6090	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2563		0.02 [-0.16, 0.21], 0.7945		-0.03 [-0.15, 0.09], 0.6201	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.0820		0.3690		0.2977	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	6/26 (23.1)	8/53 (15.1)	0/20 (0.0)	11/96 (11.5)	6/46 (13.0)
RR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0708		6.19 [0.37, 102.92], 0.2038		0.88 [0.35, 2.23], 0.7849	
OR [95%-CI]; p-value	0.25 [0.06, 1.11], 0.0543		7.11 [0.39, 129.92], 0.1281		0.86 [0.30, 2.50], 0.7854	
RD [95%-CI]; p-value	-0.16 [-0.34, 0.02], 0.0778		0.13 [0.01, 0.24], 0.0344		-0.02 [-0.13, 0.10], 0.7894	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	10/50 (20.0)	1/22 (4.5)	5/44 (11.4)	4/28 (14.3)	15/94 (16.0)	5/50 (10.0)
RR [95%-CI]; p-value	4.40 [0.60, 32.30], 0.1452		0.80 [0.23, 2.71], 0.7146		1.60 [0.62, 4.14], 0.3361	
OR [95%-CI]; p-value	5.25 [0.63, 43.84], 0.0931		0.77 [0.19, 3.15], 0.7147		1.71 [0.58, 5.01], 0.3250	
RD [95%-CI]; p-value	0.15 [0.01, 0.30], 0.0316		-0.03 [-0.19, 0.13], 0.7203		0.06 [-0.05, 0.17], 0.2943	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	9/95 (9.5)	8/48 (16.7)
RR [95%-CI]; p-value	0.50 [0.16, 1.56], 0.2328		0.68 [0.17, 2.80], 0.5941		0.57 [0.23, 1.38], 0.2119	
OR [95%-CI]; p-value	0.44 [0.11, 1.71], 0.2283		0.65 [0.13, 3.18], 0.5938		0.52 [0.19, 1.46], 0.2095	
RD [95%-CI]; p-value	-0.10 [-0.29, 0.08], 0.2673		-0.04 [-0.19, 0.11], 0.6128		-0.07 [-0.19, 0.05], 0.2430	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.6188		0.5596		0.3177	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	5/26 (19.2)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	7/46 (15.2)
RR [95%-CI]; p-value	0.36 [0.09, 1.39], 0.1398		0.94 [0.20, 4.48], 0.9415		0.55 [0.21, 1.42], 0.2148	
OR [95%-CI]; p-value	0.32 [0.07, 1.45], 0.1234		0.94 [0.17, 5.27], 0.9416		0.51 [0.17, 1.49], 0.2117	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1566		-0.01 [-0.16, 0.15], 0.9423		-0.07 [-0.19, 0.05], 0.2513	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	1/22 (4.5)	5/44 (11.4)	1/28 (3.6)	8/94 (8.5)	2/50 (4.0)
RR [95%-CI]; p-value	1.32 [0.15, 12.00], 0.8052		3.18 [0.39, 25.83], 0.2787		2.13 [0.47, 9.64], 0.3274	
OR [95%-CI]; p-value	1.34 [0.13, 13.65], 0.8040		3.46 [0.38, 31.32], 0.2435		2.23 [0.46, 10.94], 0.3107	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.7939		0.08 [-0.04, 0.19], 0.1890		0.05 [-0.03, 0.12], 0.2589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	3/24 (12.5)	5/47 (10.6)	3/24 (12.5)	8/95 (8.4)	6/48 (12.5)
RR [95%-CI]; p-value	0.50 [0.11, 2.29], 0.3725		0.85 [0.22, 3.26], 0.8141		0.67 [0.25, 1.83], 0.4388	
OR [95%-CI]; p-value	0.47 [0.09, 2.51], 0.3657		0.83 [0.18, 3.83], 0.8145		0.64 [0.21, 1.97], 0.4383	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4109		-0.02 [-0.18, 0.14], 0.8185		-0.04 [-0.15, 0.07], 0.4631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4917		0.1687		0.4286	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	4/26 (15.4)	2/53 (3.8)	1/20 (5.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.60 [0.17, 2.21], 0.4473		0.75 [0.07, 7.87], 0.8140		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.56 [0.13, 2.48], 0.4444		0.75 [0.06, 8.70], 0.8139		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.10], 0.4663		-0.01 [-0.12, 0.10], 0.8245		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	4/22 (18.2)	5/44 (11.4)	0/28 (0.0)	11/94 (11.7)	4/50 (8.0)
RR [95%-CI]; p-value	0.66 [0.21, 2.11], 0.4832		6.48 [0.37, 114.08], 0.2018		1.46 [0.49, 4.36], 0.4947	
OR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4847		7.18 [0.38, 136.81], 0.1312		1.52 [0.46, 5.06], 0.4887	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5117		0.10 [-0.01, 0.20], 0.0741		0.04 [-0.06, 0.14], 0.4653	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	1/24 (4.2)	4/47 (8.5)	6/24 (25.0)	9/95 (9.5)	7/48 (14.6)
RR [95%-CI]; p-value	2.50 [0.31, 20.22], 0.3903		0.34 [0.11, 1.09], 0.0700		0.65 [0.26, 1.64], 0.3606	
OR [95%-CI]; p-value	2.67 [0.29, 24.28], 0.3657		0.28 [0.07, 1.11], 0.0588		0.61 [0.21, 1.76], 0.3600	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.2981		-0.16 [-0.36, 0.03], 0.0902		-0.05 [-0.17, 0.06], 0.3876	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.3.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8658		0.9155		0.6005	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	6/26 (23.1)	2/53 (3.8)	0/20 (0.0)	4/96 (4.2)	6/46 (13.0)
RR [95%-CI]; p-value	0.20 [0.04, 0.93], 0.0395		1.55 [0.07, 32.89], 0.7796		0.32 [0.09, 1.08], 0.0657	
OR [95%-CI]; p-value	0.16 [0.03, 0.88], 0.0205		1.57 [0.07, 36.31], 0.7771		0.29 [0.08, 1.08], 0.0530	
RD [95%-CI]; p-value	-0.18 [-0.36, -0.01], 0.0377		0.01 [-0.07, 0.10], 0.7561		-0.09 [-0.19, 0.02], 0.0982	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	1/50 (2.0)	1/22 (4.5)	1/44 (2.3)	0/28 (0.0)	2/94 (2.1)	1/50 (2.0)
RR [95%-CI]; p-value	0.44 [0.03, 6.72], 0.5550		1.30 [0.04, 37.37], 0.8800		1.06 [0.10, 11.45], 0.9593	
OR [95%-CI]; p-value	0.43 [0.03, 7.18], 0.5449		1.30 [0.04, 40.13], 0.8796		1.07 [0.09, 12.04], 0.9593	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.6006		0.01 [-0.06, 0.07], 0.8763		0.00 [-0.05, 0.05], 0.9589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	6/95 (6.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.30 [0.08, 1.15], 0.0793		3.13 [0.16, 59.98], 0.4493		0.61 [0.19, 1.89], 0.3875	
OR [95%-CI]; p-value	0.25 [0.05, 1.17], 0.0634		3.27 [0.16, 68.07], 0.4193		0.58 [0.17, 2.01], 0.3848	
RD [95%-CI]; p-value	-0.15 [-0.32, 0.03], 0.1050		0.04 [-0.05, 0.13], 0.3419		-0.04 [-0.14, 0.06], 0.4183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_3_m_pt_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.3.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4268		0.4688		0.4917	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	2/53 (3.8)	0/20 (0.0)	5/96 (5.2)	2/46 (4.3)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		1.55 [0.07, 32.89], 0.7796		1.20 [0.24, 5.94], 0.8251	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		1.57 [0.07, 36.31], 0.7771		1.21 [0.23, 6.48], 0.8246	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		0.01 [-0.07, 0.10], 0.7561		0.01 [-0.07, 0.08], 0.8193	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	3/22 (13.6)	2/44 (4.5)	3/28 (10.7)	4/94 (4.3)	6/50 (12.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.63], 0.1616		0.42 [0.08, 2.38], 0.3300		0.35 [0.10, 1.20], 0.0952	
OR [95%-CI]; p-value	0.26 [0.04, 1.71], 0.1384		0.40 [0.06, 2.54], 0.3155		0.33 [0.09, 1.21], 0.0818	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.06], 0.2181		-0.06 [-0.19, 0.07], 0.3525		-0.08 [-0.18, 0.02], 0.1248	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	5/95 (5.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.20 [0.04, 0.96], 0.0438		3.13 [0.16, 59.98], 0.4493		0.51 [0.15, 1.66], 0.2609	
OR [95%-CI]; p-value	0.17 [0.03, 0.93], 0.0244		3.27 [0.16, 68.07], 0.4193		0.48 [0.13, 1.74], 0.2538	
RD [95%-CI]; p-value	-0.17 [-0.34, 0.01], 0.0576		0.04 [-0.05, 0.13], 0.3419		-0.05 [-0.15, 0.05], 0.2997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_3_m_pt_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.8.1.1.s6
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.8157		0.9303		0.8122	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	1/53 (1.9)	0/20 (0.0)	4/96 (4.2)	2/46 (4.3)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		0.77 [0.03, 22.19], 0.8808		0.96 [0.18, 5.04], 0.9599	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		0.77 [0.02, 23.84], 0.8806		0.96 [0.17, 5.42], 0.9599	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		-0.01 [-0.08, 0.07], 0.8870		-0.00 [-0.07, 0.07], 0.9602	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	0/22 (0.0)	3/44 (6.8)	2/28 (7.1)	6/94 (6.4)	2/50 (4.0)
RR [95%-CI]; p-value	2.70 [0.14, 51.70], 0.5096		0.95 [0.17, 5.36], 0.9579		1.60 [0.33, 7.62], 0.5579	
OR [95%-CI]; p-value	2.81 [0.13, 58.50], 0.4875		0.95 [0.15, 6.08], 0.9579		1.64 [0.32, 8.42], 0.5523	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4090		-0.00 [-0.12, 0.12], 0.9581		0.02 [-0.05, 0.10], 0.5248	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	1/24 (4.2)	1/47 (2.1)	1/24 (4.2)	3/95 (3.2)	2/48 (4.2)
RR [95%-CI]; p-value	1.00 [0.10, 10.48], 1.0000		0.51 [0.03, 7.81], 0.6292		0.76 [0.13, 4.38], 0.7569	
OR [95%-CI]; p-value	1.00 [0.09, 11.61], 1.0000		0.50 [0.03, 8.36], 0.6233		0.75 [0.12, 4.65], 0.7565	
RD [95%-CI]; p-value	0.00 [-0.10, 0.10], 1.0000		-0.02 [-0.11, 0.07], 0.6569		-0.01 [-0.08, 0.06], 0.7665	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_8_1_1_m_soc_sae5pct_ttlpth.sas using SAS 9.4

Table 12.4.8.1.2.s6
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_8_1_2_m_pt_sae5pct_ttlpth.sas using SAS 9.4

Table 12.4.5.1.1.s6
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_5_1_1_m_soc_aeg35pct_ttlpth.sas using SAS 9.4

Table 12.4.5.1.2.s6
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_5_1_2_m_pt_aeg35pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7392		0.6985		0.6210	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	3/26 (11.5)	4/53 (7.5)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.40 [0.07, 2.25], 0.3010		0.75 [0.15, 3.80], 0.7331		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.37 [0.06, 2.40], 0.2849		0.73 [0.12, 4.36], 0.7336		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3280		-0.02 [-0.17, 0.12], 0.7477		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	4/22 (18.2)	3/44 (6.8)	1/28 (3.6)	8/94 (8.5)	5/50 (10.0)
RR [95%-CI]; p-value	0.55 [0.16, 1.85], 0.3350		1.91 [0.21, 17.46], 0.5669		0.85 [0.29, 2.46], 0.7663	
OR [95%-CI]; p-value	0.50 [0.12, 2.08], 0.3336		1.98 [0.20, 20.00], 0.5577		0.84 [0.26, 2.71], 0.7665	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3766		0.03 [-0.07, 0.13], 0.5301		-0.01 [-0.12, 0.09], 0.7714	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	2/24 (8.3)	4/47 (8.5)	1/24 (4.2)	8/95 (8.4)	3/48 (6.3)
RR [95%-CI]; p-value	1.00 [0.20, 5.08], 1.0000		2.04 [0.24, 17.28], 0.5121		1.35 [0.37, 4.85], 0.6482	
OR [95%-CI]; p-value	1.00 [0.17, 5.89], 1.0000		2.14 [0.23, 20.28], 0.4986		1.38 [0.35, 5.45], 0.6455	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		0.04 [-0.07, 0.16], 0.4509		0.02 [-0.07, 0.11], 0.6301	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.7018		0.7377		0.7083	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	10/43 (23.3)	8/26 (30.8)	9/53 (17.0)	1/20 (5.0)	19/96 (19.8)	9/46 (19.6)
RR [95%-CI]; p-value	0.76 [0.34, 1.67], 0.4884		3.40 [0.46, 25.12], 0.2311		1.01 [0.50, 2.06], 0.9747	
OR [95%-CI]; p-value	0.68 [0.23, 2.03], 0.4910		3.89 [0.46, 32.86], 0.1842		1.01 [0.42, 2.46], 0.9747	
RD [95%-CI]; p-value	-0.08 [-0.29, 0.14], 0.4989		0.12 [-0.02, 0.26], 0.0913		0.00 [-0.14, 0.14], 0.9746	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	9/50 (18.0)	4/22 (18.2)	6/44 (13.6)	2/28 (7.1)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	0.99 [0.34, 2.87], 0.9853		1.91 [0.41, 8.80], 0.4070		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	0.99 [0.27, 3.63], 0.9853		2.05 [0.38, 10.97], 0.3927		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	-0.00 [-0.19, 0.19], 0.9853		0.06 [-0.07, 0.20], 0.3606		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	8/24 (33.3)	11/47 (23.4)	4/24 (16.7)	20/95 (21.1)	12/48 (25.0)
RR [95%-CI]; p-value	0.56 [0.25, 1.27], 0.1673		1.40 [0.50, 3.95], 0.5196		0.84 [0.45, 1.57], 0.5905	
OR [95%-CI]; p-value	0.46 [0.15, 1.41], 0.1696		1.53 [0.43, 5.43], 0.5106		0.80 [0.35, 1.81], 0.5928	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.07], 0.1909		0.07 [-0.12, 0.26], 0.4917		-0.04 [-0.19, 0.11], 0.5997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.3480		0.4449		0.1769	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	7/26 (26.9)	5/53 (9.4)	3/20 (15.0)	9/96 (9.4)	10/46 (21.7)
RR [95%-CI]; p-value	0.35 [0.11, 1.07], 0.0648		0.63 [0.17, 2.39], 0.4962		0.43 [0.19, 0.99], 0.0468	
OR [95%-CI]; p-value	0.28 [0.07, 1.07], 0.0527		0.59 [0.13, 2.74], 0.4971		0.37 [0.14, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.18 [-0.37, 0.02], 0.0711		-0.06 [-0.23, 0.12], 0.5334		-0.12 [-0.26, 0.01], 0.0678	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	8/50 (16.0)	3/22 (13.6)	7/44 (15.9)	3/28 (10.7)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	1.17 [0.34, 4.01], 0.7987		1.48 [0.42, 5.27], 0.5408		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	1.21 [0.29, 5.06], 0.7973		1.58 [0.37, 6.68], 0.5344		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7921		0.05 [-0.11, 0.21], 0.5180		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	5/24 (20.8)	5/47 (10.6)	5/24 (20.8)	12/95 (12.6)	10/48 (20.8)
RR [95%-CI]; p-value	0.70 [0.25, 1.98], 0.5006		0.51 [0.16, 1.59], 0.2470		0.61 [0.28, 1.30], 0.1993	
OR [95%-CI]; p-value	0.65 [0.18, 2.31], 0.5023		0.45 [0.12, 1.75], 0.2427		0.55 [0.22, 1.38], 0.1993	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5206		-0.10 [-0.29, 0.08], 0.2797		-0.08 [-0.21, 0.05], 0.2264	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2110		0.5244		0.7191	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	6/26 (23.1)	11/53 (20.8)	3/20 (15.0)	22/96 (22.9)	9/46 (19.6)
RR [95%-CI]; p-value	1.11 [0.47, 2.64], 0.8159		1.38 [0.43, 4.45], 0.5859		1.17 [0.59, 2.34], 0.6540	
OR [95%-CI]; p-value	1.15 [0.37, 3.59], 0.8150		1.48 [0.37, 5.99], 0.5775		1.22 [0.51, 2.92], 0.6510	
RD [95%-CI]; p-value	0.03 [-0.18, 0.23], 0.8134		0.06 [-0.13, 0.25], 0.5545		0.03 [-0.11, 0.18], 0.6440	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	17/50 (34.0)	5/22 (22.7)	9/44 (20.5)	8/28 (28.6)	26/94 (27.7)	13/50 (26.0)
RR [95%-CI]; p-value	1.50 [0.63, 3.54], 0.3597		0.72 [0.31, 1.64], 0.4279		1.06 [0.60, 1.88], 0.8317	
OR [95%-CI]; p-value	1.75 [0.55, 5.57], 0.3388		0.64 [0.21, 1.93], 0.4292		1.09 [0.50, 2.37], 0.8311	
RD [95%-CI]; p-value	0.11 [-0.11, 0.33], 0.3128		-0.08 [-0.29, 0.12], 0.4387		0.02 [-0.13, 0.17], 0.8300	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	9/24 (37.5)	13/47 (27.7)	5/24 (20.8)	23/95 (24.2)	14/48 (29.2)
RR [95%-CI]; p-value	0.56 [0.26, 1.18], 0.1273		1.33 [0.54, 3.29], 0.5401		0.83 [0.47, 1.46], 0.5194	
OR [95%-CI]; p-value	0.44 [0.15, 1.29], 0.1304		1.45 [0.45, 4.70], 0.5317		0.78 [0.36, 1.69], 0.5228	
RD [95%-CI]; p-value	-0.17 [-0.39, 0.06], 0.1469		0.07 [-0.14, 0.28], 0.5176		-0.05 [-0.20, 0.11], 0.5302	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.3456		0.5882		0.6032	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	7/96 (7.3)	3/46 (6.5)
RR [95%-CI]; p-value	1.51 [0.32, 7.24], 0.6050		0.75 [0.07, 7.87], 0.8140		1.12 [0.30, 4.13], 0.8670	
OR [95%-CI]; p-value	1.58 [0.28, 8.80], 0.5998		0.75 [0.06, 8.70], 0.8139		1.13 [0.28, 4.57], 0.8667	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5823		-0.01 [-0.12, 0.10], 0.8245		0.01 [-0.08, 0.10], 0.8643	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	3/22 (13.6)	4/44 (9.1)	0/28 (0.0)	9/94 (9.6)	3/50 (6.0)
RR [95%-CI]; p-value	0.73 [0.19, 2.80], 0.6502		5.18 [0.28, 94.36], 0.2665		1.60 [0.45, 5.63], 0.4675	
OR [95%-CI]; p-value	0.70 [0.15, 3.24], 0.6511		5.60 [0.28, 110.18], 0.2060		1.66 [0.43, 6.43], 0.4600	
RD [95%-CI]; p-value	-0.04 [-0.20, 0.13], 0.6672		0.07 [-0.02, 0.17], 0.1409		0.04 [-0.05, 0.12], 0.4297	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	0/24 (0.0)	5/47 (10.6)	2/24 (8.3)	12/95 (12.6)	2/48 (4.2)
RR [95%-CI]; p-value	7.15 [0.42, 120.79], 0.1728		1.28 [0.27, 6.10], 0.7596		3.03 [0.71, 13.00], 0.1355	
OR [95%-CI]; p-value	8.20 [0.45, 150.89], 0.0972		1.31 [0.23, 7.31], 0.7579		3.33 [0.71, 15.51], 0.1077	
RD [95%-CI]; p-value	0.13 [0.01, 0.24], 0.0318		0.02 [-0.12, 0.16], 0.7494		0.08 [-0.00, 0.17], 0.0580	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.4574		0.7323		0.4402	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	4/26 (15.4)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	6/46 (13.0)
RR [95%-CI]; p-value	0.45 [0.11, 1.87], 0.2736		0.94 [0.20, 4.48], 0.9415		0.64 [0.24, 1.73], 0.3791	
OR [95%-CI]; p-value	0.41 [0.08, 2.01], 0.2623		0.94 [0.17, 5.27], 0.9416		0.61 [0.20, 1.86], 0.3783	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2976		-0.01 [-0.16, 0.15], 0.9423		-0.05 [-0.16, 0.06], 0.4095	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	1/22 (4.5)	5/44 (11.4)	2/28 (7.1)	10/94 (10.6)	3/50 (6.0)
RR [95%-CI]; p-value	2.20 [0.27, 17.75], 0.4592		1.59 [0.33, 7.65], 0.5621		1.77 [0.51, 6.15], 0.3668	
OR [95%-CI]; p-value	2.33 [0.26, 21.24], 0.4405		1.67 [0.30, 9.25], 0.5556		1.87 [0.49, 7.11], 0.3551	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3745		0.04 [-0.09, 0.18], 0.5363		0.05 [-0.04, 0.14], 0.3160	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	13/95 (13.7)	8/48 (16.7)
RR [95%-CI]; p-value	0.90 [0.34, 2.39], 0.8326		0.68 [0.17, 2.80], 0.5941		0.82 [0.37, 1.84], 0.6331	
OR [95%-CI]; p-value	0.88 [0.26, 2.98], 0.8332		0.65 [0.13, 3.18], 0.5938		0.79 [0.30, 2.07], 0.6342	
RD [95%-CI]; p-value	-0.02 [-0.22, 0.18], 0.8353		-0.04 [-0.19, 0.11], 0.6128		-0.03 [-0.16, 0.10], 0.6429	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.2418		0.4047		0.4582	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	9/26 (34.6)	8/53 (15.1)	2/20 (10.0)	13/96 (13.5)	11/46 (23.9)
RR [95%-CI]; p-value	0.34 [0.13, 0.89], 0.0289		1.51 [0.35, 6.51], 0.5809		0.57 [0.28, 1.17], 0.1226	
OR [95%-CI]; p-value	0.25 [0.07, 0.85], 0.0214		1.60 [0.31, 8.27], 0.5724		0.50 [0.20, 1.22], 0.1228	
RD [95%-CI]; p-value	-0.23 [-0.44, -0.02], 0.0291		0.05 [-0.11, 0.21], 0.5402		-0.10 [-0.24, 0.04], 0.1494	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	13/50 (26.0)	7/22 (31.8)	7/44 (15.9)	3/28 (10.7)	20/94 (21.3)	10/50 (20.0)
RR [95%-CI]; p-value	0.82 [0.38, 1.76], 0.6072		1.48 [0.42, 5.27], 0.5408		1.06 [0.54, 2.09], 0.8579	
OR [95%-CI]; p-value	0.75 [0.25, 2.26], 0.6116		1.58 [0.37, 6.68], 0.5344		1.08 [0.46, 2.53], 0.8575	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.17], 0.6192		0.05 [-0.11, 0.21], 0.5180		0.01 [-0.13, 0.15], 0.8565	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	5/24 (20.8)	10/47 (21.3)	8/24 (33.3)	20/95 (21.1)	13/48 (27.1)
RR [95%-CI]; p-value	1.00 [0.38, 2.60], 1.0000		0.64 [0.29, 1.41], 0.2648		0.78 [0.42, 1.42], 0.4152	
OR [95%-CI]; p-value	1.00 [0.30, 3.34], 1.0000		0.54 [0.18, 1.62], 0.2693		0.72 [0.32, 1.61], 0.4189	
RD [95%-CI]; p-value	0.00 [-0.20, 0.20], 1.0000		-0.12 [-0.34, 0.10], 0.2870		-0.06 [-0.21, 0.09], 0.4310	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3193		0.1824		0.0755	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	8/26 (30.8)	13/53 (24.5)	3/20 (15.0)	24/96 (25.0)	11/46 (23.9)
RR [95%-CI]; p-value	0.83 [0.39, 1.79], 0.6382		1.64 [0.52, 5.14], 0.4000		1.05 [0.56, 1.95], 0.8884	
OR [95%-CI]; p-value	0.77 [0.26, 2.27], 0.6402		1.84 [0.46, 7.30], 0.3801		1.06 [0.47, 2.41], 0.8881	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.17], 0.6442		0.10 [-0.10, 0.29], 0.3375		0.01 [-0.14, 0.16], 0.8875	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	7/22 (31.8)	4/44 (9.1)	7/28 (25.0)	9/94 (9.6)	14/50 (28.0)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		0.36 [0.12, 1.13], 0.0802		0.34 [0.16, 0.73], 0.0059	
OR [95%-CI]; p-value	0.24 [0.07, 0.86], 0.0221		0.30 [0.08, 1.14], 0.0674		0.27 [0.11, 0.69], 0.0041	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0433		-0.16 [-0.34, 0.02], 0.0858		-0.18 [-0.32, -0.05], 0.0088	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	8/24 (33.3)	5/47 (10.6)	4/24 (16.7)	13/95 (13.7)	12/48 (25.0)
RR [95%-CI]; p-value	0.50 [0.21, 1.17], 0.1094		0.64 [0.19, 2.16], 0.4705		0.55 [0.27, 1.11], 0.0932	
OR [95%-CI]; p-value	0.40 [0.13, 1.25], 0.1088		0.60 [0.14, 2.46], 0.4702		0.48 [0.20, 1.14], 0.0925	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.05], 0.1306		-0.06 [-0.23, 0.11], 0.4951		-0.11 [-0.25, 0.03], 0.1148	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.6254		0.6749		0.5805	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	4/26 (15.4)	5/53 (9.4)	0/20 (0.0)	10/96 (10.4)	4/46 (8.7)
RR [95%-CI]; p-value	0.76 [0.22, 2.56], 0.6532		3.87 [0.22, 67.68], 0.3543		1.20 [0.40, 3.62], 0.7487	
OR [95%-CI]; p-value	0.72 [0.18, 2.98], 0.6534		4.17 [0.22, 79.89], 0.3067		1.22 [0.36, 4.12], 0.7475	
RD [95%-CI]; p-value	-0.04 [-0.21, 0.13], 0.6622		0.07 [-0.03, 0.17], 0.1841		0.02 [-0.08, 0.12], 0.7404	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	6/22 (27.3)	6/44 (13.6)	4/28 (14.3)	11/94 (11.7)	10/50 (20.0)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0675		0.95 [0.30, 3.09], 0.9380		0.59 [0.27, 1.28], 0.1806	
OR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0606		0.95 [0.24, 3.71], 0.9381		0.53 [0.21, 1.35], 0.1792	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.03], 0.0967		-0.01 [-0.17, 0.16], 0.9384		-0.08 [-0.21, 0.05], 0.2057	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	3/24 (12.5)	9/47 (19.1)	4/24 (16.7)	11/95 (11.6)	7/48 (14.6)
RR [95%-CI]; p-value	0.33 [0.06, 1.86], 0.2108		1.15 [0.39, 3.35], 0.7993		0.79 [0.33, 1.92], 0.6081	
OR [95%-CI]; p-value	0.30 [0.05, 1.96], 0.1898		1.18 [0.32, 4.33], 0.7981		0.77 [0.28, 2.12], 0.6090	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2563		0.02 [-0.16, 0.21], 0.7945		-0.03 [-0.15, 0.09], 0.6201	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.9523		0.9874		0.9506	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	5/96 (5.2)	3/46 (6.5)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		0.75 [0.07, 7.87], 0.8140		0.80 [0.20, 3.20], 0.7507	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		0.75 [0.06, 8.70], 0.8139		0.79 [0.18, 3.45], 0.7507	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		-0.01 [-0.12, 0.10], 0.8245		-0.01 [-0.10, 0.07], 0.7594	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	1/22 (4.5)	3/44 (6.8)	2/28 (7.1)	6/94 (6.4)	3/50 (6.0)
RR [95%-CI]; p-value	1.32 [0.15, 12.00], 0.8052		0.95 [0.17, 5.36], 0.9579		1.06 [0.28, 4.07], 0.9280	
OR [95%-CI]; p-value	1.34 [0.13, 13.65], 0.8040		0.95 [0.15, 6.08], 0.9579		1.07 [0.26, 4.47], 0.9280	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.7939		-0.00 [-0.12, 0.12], 0.9581		0.00 [-0.08, 0.09], 0.9273	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	2/24 (8.3)	7/47 (14.9)	4/24 (16.7)	12/95 (12.6)	6/48 (12.5)
RR [95%-CI]; p-value	1.25 [0.26, 5.98], 0.7799		0.89 [0.29, 2.75], 0.8447		1.01 [0.40, 2.53], 0.9821	
OR [95%-CI]; p-value	1.28 [0.23, 7.13], 0.7785		0.88 [0.23, 3.34], 0.8451		1.01 [0.35, 2.89], 0.9821	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7711		-0.02 [-0.20, 0.16], 0.8474		0.00 [-0.11, 0.12], 0.9821	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.0820		0.3690		0.2977	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	6/26 (23.1)	8/53 (15.1)	0/20 (0.0)	11/96 (11.5)	6/46 (13.0)
RR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0708		6.19 [0.37, 102.92], 0.2038		0.88 [0.35, 2.23], 0.7849	
OR [95%-CI]; p-value	0.25 [0.06, 1.11], 0.0543		7.11 [0.39, 129.92], 0.1281		0.86 [0.30, 2.50], 0.7854	
RD [95%-CI]; p-value	-0.16 [-0.34, 0.02], 0.0778		0.13 [0.01, 0.24], 0.0344		-0.02 [-0.13, 0.10], 0.7894	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	10/50 (20.0)	1/22 (4.5)	5/44 (11.4)	4/28 (14.3)	15/94 (16.0)	5/50 (10.0)
RR [95%-CI]; p-value	4.40 [0.60, 32.30], 0.1452		0.80 [0.23, 2.71], 0.7146		1.60 [0.62, 4.14], 0.3361	
OR [95%-CI]; p-value	5.25 [0.63, 43.84], 0.0931		0.77 [0.19, 3.15], 0.7147		1.71 [0.58, 5.01], 0.3250	
RD [95%-CI]; p-value	0.15 [0.01, 0.30], 0.0316		-0.03 [-0.19, 0.13], 0.7203		0.06 [-0.05, 0.17], 0.2943	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	9/95 (9.5)	8/48 (16.7)
RR [95%-CI]; p-value	0.50 [0.16, 1.56], 0.2328		0.68 [0.17, 2.80], 0.5941		0.57 [0.23, 1.38], 0.2119	
OR [95%-CI]; p-value	0.44 [0.11, 1.71], 0.2283		0.65 [0.13, 3.18], 0.5938		0.52 [0.19, 1.46], 0.2095	
RD [95%-CI]; p-value	-0.10 [-0.29, 0.08], 0.2673		-0.04 [-0.19, 0.11], 0.6128		-0.07 [-0.19, 0.05], 0.2430	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.6188		0.5596		0.3177	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	5/26 (19.2)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	7/46 (15.2)
RR [95%-CI]; p-value	0.36 [0.09, 1.39], 0.1398		0.94 [0.20, 4.48], 0.9415		0.55 [0.21, 1.42], 0.2148	
OR [95%-CI]; p-value	0.32 [0.07, 1.45], 0.1234		0.94 [0.17, 5.27], 0.9416		0.51 [0.17, 1.49], 0.2117	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1566		-0.01 [-0.16, 0.15], 0.9423		-0.07 [-0.19, 0.05], 0.2513	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	1/22 (4.5)	5/44 (11.4)	1/28 (3.6)	8/94 (8.5)	2/50 (4.0)
RR [95%-CI]; p-value	1.32 [0.15, 12.00], 0.8052		3.18 [0.39, 25.83], 0.2787		2.13 [0.47, 9.64], 0.3274	
OR [95%-CI]; p-value	1.34 [0.13, 13.65], 0.8040		3.46 [0.38, 31.32], 0.2435		2.23 [0.46, 10.94], 0.3107	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.7939		0.08 [-0.04, 0.19], 0.1890		0.05 [-0.03, 0.12], 0.2589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	3/24 (12.5)	5/47 (10.6)	3/24 (12.5)	8/95 (8.4)	6/48 (12.5)
RR [95%-CI]; p-value	0.50 [0.11, 2.29], 0.3725		0.85 [0.22, 3.26], 0.8141		0.67 [0.25, 1.83], 0.4388	
OR [95%-CI]; p-value	0.47 [0.09, 2.51], 0.3657		0.83 [0.18, 3.83], 0.8145		0.64 [0.21, 1.97], 0.4383	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4109		-0.02 [-0.18, 0.14], 0.8185		-0.04 [-0.15, 0.07], 0.4631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4917		0.1687		0.4286	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	4/26 (15.4)	2/53 (3.8)	1/20 (5.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.60 [0.17, 2.21], 0.4473		0.75 [0.07, 7.87], 0.8140		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.56 [0.13, 2.48], 0.4444		0.75 [0.06, 8.70], 0.8139		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.10], 0.4663		-0.01 [-0.12, 0.10], 0.8245		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	4/22 (18.2)	5/44 (11.4)	0/28 (0.0)	11/94 (11.7)	4/50 (8.0)
RR [95%-CI]; p-value	0.66 [0.21, 2.11], 0.4832		6.48 [0.37, 114.08], 0.2018		1.46 [0.49, 4.36], 0.4947	
OR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4847		7.18 [0.38, 136.81], 0.1312		1.52 [0.46, 5.06], 0.4887	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5117		0.10 [-0.01, 0.20], 0.0741		0.04 [-0.06, 0.14], 0.4653	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	1/24 (4.2)	4/47 (8.5)	6/24 (25.0)	9/95 (9.5)	7/48 (14.6)
RR [95%-CI]; p-value	2.50 [0.31, 20.22], 0.3903		0.34 [0.11, 1.09], 0.0700		0.65 [0.26, 1.64], 0.3606	
OR [95%-CI]; p-value	2.67 [0.29, 24.28], 0.3657		0.28 [0.07, 1.11], 0.0588		0.61 [0.21, 1.76], 0.3600	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.2981		-0.16 [-0.36, 0.03], 0.0902		-0.05 [-0.17, 0.06], 0.3876	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.4.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8658		0.9155		0.6005	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	6/26 (23.1)	2/53 (3.8)	0/20 (0.0)	4/96 (4.2)	6/46 (13.0)
RR [95%-CI]; p-value	0.20 [0.04, 0.93], 0.0395		1.55 [0.07, 32.89], 0.7796		0.32 [0.09, 1.08], 0.0657	
OR [95%-CI]; p-value	0.16 [0.03, 0.88], 0.0205		1.57 [0.07, 36.31], 0.7771		0.29 [0.08, 1.08], 0.0530	
RD [95%-CI]; p-value	-0.18 [-0.36, -0.01], 0.0377		0.01 [-0.07, 0.10], 0.7561		-0.09 [-0.19, 0.02], 0.0982	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	1/50 (2.0)	1/22 (4.5)	1/44 (2.3)	0/28 (0.0)	2/94 (2.1)	1/50 (2.0)
RR [95%-CI]; p-value	0.44 [0.03, 6.72], 0.5550		1.30 [0.04, 37.37], 0.8800		1.06 [0.10, 11.45], 0.9593	
OR [95%-CI]; p-value	0.43 [0.03, 7.18], 0.5449		1.30 [0.04, 40.13], 0.8796		1.07 [0.09, 12.04], 0.9593	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.6006		0.01 [-0.06, 0.07], 0.8763		0.00 [-0.05, 0.05], 0.9589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	6/95 (6.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.30 [0.08, 1.15], 0.0793		3.13 [0.16, 59.98], 0.4493		0.61 [0.19, 1.89], 0.3875	
OR [95%-CI]; p-value	0.25 [0.05, 1.17], 0.0634		3.27 [0.16, 68.07], 0.4193		0.58 [0.17, 2.01], 0.3848	
RD [95%-CI]; p-value	-0.15 [-0.32, 0.03], 0.1050		0.04 [-0.05, 0.13], 0.3419		-0.04 [-0.14, 0.06], 0.4183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_4_m_pt_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.4.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4268		0.4688		0.4917	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	2/53 (3.8)	0/20 (0.0)	5/96 (5.2)	2/46 (4.3)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		1.55 [0.07, 32.89], 0.7796		1.20 [0.24, 5.94], 0.8251	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		1.57 [0.07, 36.31], 0.7771		1.21 [0.23, 6.48], 0.8246	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		0.01 [-0.07, 0.10], 0.7561		0.01 [-0.07, 0.08], 0.8193	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	3/22 (13.6)	2/44 (4.5)	3/28 (10.7)	4/94 (4.3)	6/50 (12.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.63], 0.1616		0.42 [0.08, 2.38], 0.3300		0.35 [0.10, 1.20], 0.0952	
OR [95%-CI]; p-value	0.26 [0.04, 1.71], 0.1384		0.40 [0.06, 2.54], 0.3155		0.33 [0.09, 1.21], 0.0818	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.06], 0.2181		-0.06 [-0.19, 0.07], 0.3525		-0.08 [-0.18, 0.02], 0.1248	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	5/95 (5.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.20 [0.04, 0.96], 0.0438		3.13 [0.16, 59.98], 0.4493		0.51 [0.15, 1.66], 0.2609	
OR [95%-CI]; p-value	0.17 [0.03, 0.93], 0.0244		3.27 [0.16, 68.07], 0.4193		0.48 [0.13, 1.74], 0.2538	
RD [95%-CI]; p-value	-0.17 [-0.34, 0.01], 0.0576		0.04 [-0.05, 0.13], 0.3419		-0.05 [-0.15, 0.05], 0.2997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_4_m_pt_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.4.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.4190		0.3717		0.1901	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	3/26 (11.5)	1/53 (1.9)	1/20 (5.0)	3/96 (3.1)	4/46 (8.7)
RR [95%-CI]; p-value	0.40 [0.07, 2.25], 0.3010		0.38 [0.02, 5.75], 0.4831		0.36 [0.08, 1.54], 0.1681	
OR [95%-CI]; p-value	0.37 [0.06, 2.40], 0.2849		0.37 [0.02, 6.14], 0.4674		0.34 [0.07, 1.58], 0.1513	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3280		-0.03 [-0.13, 0.07], 0.5509		-0.06 [-0.14, 0.03], 0.2176	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	4/50 (8.0)	1/22 (4.5)	3/44 (6.8)	0/28 (0.0)	7/94 (7.4)	1/50 (2.0)
RR [95%-CI]; p-value	1.76 [0.21, 14.86], 0.6035		3.89 [0.20, 74.74], 0.3682		3.72 [0.47, 29.42], 0.2126	
OR [95%-CI]; p-value	1.83 [0.19, 17.35], 0.5953		4.10 [0.20, 85.00], 0.3259		3.94 [0.47, 32.99], 0.1743	
RD [95%-CI]; p-value	0.03 [-0.08, 0.15], 0.5561		0.05 [-0.04, 0.14], 0.2632		0.05 [-0.01, 0.12], 0.1044	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	1/24 (4.2)	4/47 (8.5)	5/24 (20.8)	8/95 (8.4)	6/48 (12.5)
RR [95%-CI]; p-value	2.00 [0.24, 16.93], 0.5247		0.41 [0.12, 1.38], 0.1502		0.67 [0.25, 1.83], 0.4388	
OR [95%-CI]; p-value	2.09 [0.22, 19.81], 0.5121		0.35 [0.09, 1.46], 0.1399		0.64 [0.21, 1.97], 0.4383	
RD [95%-CI]; p-value	0.04 [-0.07, 0.15], 0.4652		-0.12 [-0.30, 0.06], 0.1821		-0.04 [-0.15, 0.07], 0.4631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_4_m_pt_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.1368		0.8007		0.2227	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	1/43 (2.3)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	3/96 (3.1)	3/46 (6.5)
RR [95%-CI]; p-value	0.30 [0.03, 3.17], 0.3185		0.75 [0.07, 7.87], 0.8140		0.48 [0.10, 2.28], 0.3557	
OR [95%-CI]; p-value	0.29 [0.02, 3.32], 0.2895		0.75 [0.06, 8.70], 0.8139		0.46 [0.09, 2.39], 0.3464	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3472		-0.01 [-0.12, 0.10], 0.8245		-0.03 [-0.11, 0.05], 0.4017	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	0/22 (0.0)	1/44 (2.3)	2/28 (7.1)	3/94 (3.2)	2/50 (4.0)
RR [95%-CI]; p-value	1.80 [0.08, 38.34], 0.7064		0.32 [0.03, 3.35], 0.3402		0.80 [0.14, 4.62], 0.8010	
OR [95%-CI]; p-value	1.83 [0.08, 42.35], 0.7011		0.30 [0.03, 3.50], 0.3134		0.79 [0.13, 4.90], 0.8008	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6694		-0.05 [-0.15, 0.06], 0.3636		-0.01 [-0.07, 0.06], 0.8071	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	12/48 (25.0)	0/24 (0.0)	6/47 (12.8)	4/24 (16.7)	18/95 (18.9)	4/48 (8.3)
RR [95%-CI]; p-value	12.25 [0.75, 198.80], 0.0780		0.77 [0.24, 2.46], 0.6539		2.27 [0.81, 6.35], 0.1167	
OR [95%-CI]; p-value	16.00 [0.90, 283.81], 0.0144		0.73 [0.19, 2.89], 0.6549		2.57 [0.82, 8.08], 0.0967	
RD [95%-CI]; p-value	0.23 [0.09, 0.36], 0.0008		-0.04 [-0.22, 0.14], 0.6658		0.11 [-0.00, 0.22], 0.0609	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8042		0.8719		0.5343	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	0/26 (0.0)	0/53 (0.0)	0/20 (0.0)	0/96 (0.0)	0/46 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	0/44 (0.0)	1/28 (3.6)	0/94 (0.0)	1/50 (2.0)
RR [95%-CI]; p-value	NA		0.31 [0.01, 9.07], 0.5002		0.26 [0.01, 7.75], 0.4403	
OR [95%-CI]; p-value	NA		0.31 [0.01, 9.46], 0.4759		0.26 [0.01, 7.91], 0.4066	
RD [95%-CI]; p-value	NA		-0.02 [-0.10, 0.05], 0.5245		-0.01 [-0.06, 0.03], 0.4869	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	0/24 (0.0)	1/47 (2.1)	0/24 (0.0)	3/95 (3.2)	0/48 (0.0)
RR [95%-CI]; p-value	2.04 [0.10, 43.57], 0.6476		1.04 [0.04, 30.00], 0.9806		3.06 [0.16, 59.94], 0.4606	
OR [95%-CI]; p-value	2.09 [0.09, 48.12], 0.6389		1.04 [0.03, 32.23], 0.9806		3.13 [0.15, 63.77], 0.4346	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6005		0.00 [-0.07, 0.07], 0.9805		0.02 [-0.02, 0.07], 0.3566	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.1657		0.9920		0.3503	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	1/43 (2.3)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	3/96 (3.1)	3/46 (6.5)
RR [95%-CI]; p-value	0.30 [0.03, 3.17], 0.3185		0.75 [0.07, 7.87], 0.8140		0.48 [0.10, 2.28], 0.3557	
OR [95%-CI]; p-value	0.29 [0.02, 3.32], 0.2895		0.75 [0.06, 8.70], 0.8139		0.46 [0.09, 2.39], 0.3464	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3472		-0.01 [-0.12, 0.10], 0.8245		-0.03 [-0.11, 0.05], 0.4017	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	0/22 (0.0)	1/44 (2.3)	1/28 (3.6)	3/94 (3.2)	1/50 (2.0)
RR [95%-CI]; p-value	1.80 [0.08, 38.34], 0.7064		0.64 [0.04, 9.77], 0.7457		1.60 [0.17, 14.94], 0.6822	
OR [95%-CI]; p-value	1.83 [0.08, 42.35], 0.7011		0.63 [0.04, 10.46], 0.7437		1.62 [0.16, 15.95], 0.6787	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6694		-0.01 [-0.09, 0.07], 0.7552		0.01 [-0.04, 0.06], 0.6572	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	0/24 (0.0)	5/47 (10.6)	4/24 (16.7)	15/95 (15.8)	4/48 (8.3)
RR [95%-CI]; p-value	10.21 [0.62, 167.58], 0.1037		0.64 [0.19, 2.16], 0.4705		1.89 [0.67, 5.40], 0.2315	
OR [95%-CI]; p-value	12.63 [0.70, 226.35], 0.0315		0.60 [0.14, 2.46], 0.4702		2.06 [0.64, 6.60], 0.2148	
RD [95%-CI]; p-value	0.19 [0.06, 0.32], 0.0040		-0.06 [-0.23, 0.11], 0.4951		0.07 [-0.03, 0.18], 0.1728	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.6393		0.7957		0.4225	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	1/43 (2.3)	1/26 (3.8)	0/53 (0.0)	0/20 (0.0)	1/96 (1.0)	1/46 (2.2)
RR [95%-CI]; p-value	0.60 [0.04, 9.26], 0.7178		NA		0.48 [0.03, 7.49], 0.6000	
OR [95%-CI]; p-value	0.60 [0.04, 9.94], 0.7152		NA		0.47 [0.03, 7.75], 0.5921	
RD [95%-CI]; p-value	-0.02 [-0.10, 0.07], 0.7306		NA		-0.01 [-0.06, 0.04], 0.6352	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	0/22 (0.0)	1/44 (2.3)	0/28 (0.0)	3/94 (3.2)	0/50 (0.0)
RR [95%-CI]; p-value	1.80 [0.08, 38.34], 0.7064		1.30 [0.04, 37.37], 0.8800		3.22 [0.16, 63.10], 0.4405	
OR [95%-CI]; p-value	1.83 [0.08, 42.35], 0.7011		1.30 [0.04, 40.13], 0.8796		3.30 [0.16, 67.13], 0.4118	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6694		0.01 [-0.06, 0.07], 0.8763		0.02 [-0.02, 0.07], 0.3357	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	0/24 (0.0)	2/47 (4.3)	0/24 (0.0)	6/95 (6.3)	0/48 (0.0)
RR [95%-CI]; p-value	4.08 [0.22, 74.17], 0.3416		2.09 [0.10, 44.48], 0.6379		6.13 [0.35, 107.42], 0.2148	
OR [95%-CI]; p-value	4.36 [0.22, 86.06], 0.2936		2.13 [0.09, 49.21], 0.6285		6.47 [0.35, 118.36], 0.1499	
RD [95%-CI]; p-value	0.06 [-0.03, 0.16], 0.1997		0.02 [-0.06, 0.10], 0.5893		0.05 [-0.00, 0.11], 0.0671	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.1910		0.3152		0.0481	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	4/26 (15.4)	3/53 (5.7)	2/20 (10.0)	3/96 (3.1)	6/46 (13.0)
RR [95%-CI]; p-value	0.07 [0.00, 1.36], 0.0795		0.57 [0.10, 3.14], 0.5151		0.24 [0.06, 0.92], 0.0367	
OR [95%-CI]; p-value	0.06 [0.00, 1.26], 0.0196		0.54 [0.08, 3.50], 0.5127		0.22 [0.05, 0.90], 0.0232	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0498		-0.04 [-0.19, 0.10], 0.5587		-0.10 [-0.20, 0.00], 0.0600	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	7/50 (14.0)	2/22 (9.1)	6/44 (13.6)	1/28 (3.6)	13/94 (13.8)	3/50 (6.0)
RR [95%-CI]; p-value	1.54 [0.35, 6.83], 0.5699		3.82 [0.49, 30.06], 0.2031		2.30 [0.69, 7.71], 0.1753	
OR [95%-CI]; p-value	1.63 [0.31, 8.55], 0.5618		4.26 [0.48, 37.48], 0.1599		2.51 [0.68, 9.28], 0.1546	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5318		0.10 [-0.02, 0.22], 0.1073		0.08 [-0.02, 0.17], 0.1097	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	3/24 (12.5)	4/47 (8.5)	3/24 (12.5)	9/95 (9.5)	6/48 (12.5)
RR [95%-CI]; p-value	0.83 [0.22, 3.20], 0.7905		0.68 [0.17, 2.80], 0.5941		0.76 [0.29, 2.01], 0.5765	
OR [95%-CI]; p-value	0.81 [0.18, 3.73], 0.7909		0.65 [0.13, 3.18], 0.5938		0.73 [0.24, 2.19], 0.5770	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.14], 0.7961		-0.04 [-0.19, 0.11], 0.6128		-0.03 [-0.14, 0.08], 0.5916	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8042		0.7315		0.9433	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	0/26 (0.0)	1/53 (1.9)	0/20 (0.0)	1/96 (1.0)	0/46 (0.0)
RR [95%-CI]; p-value	NA		0.77 [0.03, 22.19], 0.8808		0.97 [0.03, 28.36], 0.9853	
OR [95%-CI]; p-value	NA		0.77 [0.02, 23.84], 0.8806		0.97 [0.03, 29.40], 0.9853	
RD [95%-CI]; p-value	NA		-0.01 [-0.08, 0.07], 0.8870		-0.00 [-0.04, 0.04], 0.9854	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	2/44 (4.5)	0/28 (0.0)	2/94 (2.1)	0/50 (0.0)
RR [95%-CI]; p-value	NA		2.59 [0.12, 55.42], 0.5424		2.15 [0.10, 46.76], 0.6264	
OR [95%-CI]; p-value	NA		2.67 [0.12, 61.34], 0.5247		2.17 [0.10, 49.14], 0.6170	
RD [95%-CI]; p-value	NA		0.03 [-0.05, 0.11], 0.4841		0.01 [-0.03, 0.05], 0.5769	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	0/24 (0.0)	1/47 (2.1)	1/24 (4.2)	3/95 (3.2)	1/48 (2.1)
RR [95%-CI]; p-value	2.04 [0.10, 43.57], 0.6476		0.51 [0.03, 7.81], 0.6292		1.52 [0.16, 14.19], 0.7155	
OR [95%-CI]; p-value	2.09 [0.09, 48.12], 0.6389		0.50 [0.03, 8.36], 0.6233		1.53 [0.16, 15.14], 0.7129	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6005		-0.02 [-0.11, 0.07], 0.6569		0.01 [-0.04, 0.06], 0.6942	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.1704		0.2756		0.0309	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	4/26 (15.4)	2/53 (3.8)	2/20 (10.0)	2/96 (2.1)	6/46 (13.0)
RR [95%-CI]; p-value	0.07 [0.00, 1.36], 0.0795		0.38 [0.06, 2.50], 0.3125		0.16 [0.03, 0.76], 0.0213	
OR [95%-CI]; p-value	0.06 [0.00, 1.26], 0.0196		0.35 [0.05, 2.69], 0.2972		0.14 [0.03, 0.73], 0.0080	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0498		-0.06 [-0.20, 0.08], 0.3872		-0.11 [-0.21, -0.01], 0.0342	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	7/50 (14.0)	2/22 (9.1)	5/44 (11.4)	1/28 (3.6)	12/94 (12.8)	3/50 (6.0)
RR [95%-CI]; p-value	1.54 [0.35, 6.83], 0.5699		3.18 [0.39, 25.83], 0.2787		2.13 [0.63, 7.19], 0.2243	
OR [95%-CI]; p-value	1.63 [0.31, 8.55], 0.5618		3.46 [0.38, 31.32], 0.2435		2.29 [0.62, 8.54], 0.2057	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5318		0.08 [-0.04, 0.19], 0.1890		0.07 [-0.03, 0.16], 0.1595	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	3/24 (12.5)	3/47 (6.4)	3/24 (12.5)	6/95 (6.3)	6/48 (12.5)
RR [95%-CI]; p-value	0.50 [0.11, 2.29], 0.3725		0.51 [0.11, 2.34], 0.3870		0.51 [0.17, 1.48], 0.2141	
OR [95%-CI]; p-value	0.47 [0.09, 2.51], 0.3657		0.48 [0.09, 2.57], 0.3807		0.47 [0.14, 1.55], 0.2078	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4109		-0.06 [-0.21, 0.09], 0.4230		-0.06 [-0.17, 0.04], 0.2509	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8290		0.4836		0.6201	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	0/26 (0.0)	2/53 (3.8)	0/20 (0.0)	2/96 (2.1)	0/46 (0.0)
RR [95%-CI]; p-value	NA		1.55 [0.07, 32.89], 0.7796		1.94 [0.09, 42.12], 0.6738	
OR [95%-CI]; p-value	NA		1.57 [0.07, 36.31], 0.7771		1.96 [0.09, 44.28], 0.6674	
RD [95%-CI]; p-value	NA		0.01 [-0.07, 0.10], 0.7561		0.01 [-0.03, 0.05], 0.6313	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	0/22 (0.0)	3/44 (6.8)	0/28 (0.0)	6/94 (6.4)	0/50 (0.0)
RR [95%-CI]; p-value	2.70 [0.14, 51.70], 0.5096		3.89 [0.20, 74.74], 0.3682		6.45 [0.37, 113.10], 0.2023	
OR [95%-CI]; p-value	2.81 [0.13, 58.50], 0.4875		4.10 [0.20, 85.00], 0.3259		6.82 [0.37, 124.63], 0.1359	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4090		0.05 [-0.04, 0.14], 0.2632		0.05 [-0.00, 0.11], 0.0612	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	0/24 (0.0)	0/47 (0.0)	1/24 (4.2)	2/95 (2.1)	1/48 (2.1)
RR [95%-CI]; p-value	2.04 [0.10, 43.57], 0.6476		0.25 [0.01, 7.27], 0.4221		1.01 [0.09, 10.87], 0.9931	
OR [95%-CI]; p-value	2.09 [0.09, 48.12], 0.6389		0.24 [0.01, 7.56], 0.3856		1.01 [0.09, 11.43], 0.9931	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6005		-0.03 [-0.12, 0.05], 0.4730		0.00 [-0.05, 0.05], 0.9931	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.6.s6
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.9131		0.6583		0.7402	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	7/43 (16.3)	7/26 (26.9)	10/53 (18.9)	2/20 (10.0)	17/96 (17.7)	9/46 (19.6)
RR [95%-CI]; p-value	0.60 [0.24, 1.53], 0.2878		1.89 [0.45, 7.87], 0.3837		0.91 [0.44, 1.87], 0.7882	
OR [95%-CI]; p-value	0.53 [0.16, 1.73], 0.2867		2.09 [0.42, 10.52], 0.3619		0.88 [0.36, 2.17], 0.7889	
RD [95%-CI]; p-value	-0.11 [-0.31, 0.10], 0.3043		0.09 [-0.08, 0.26], 0.3022		-0.02 [-0.16, 0.12], 0.7916	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	4/22 (18.2)	4/44 (9.1)	3/28 (10.7)	10/94 (10.6)	7/50 (14.0)
RR [95%-CI]; p-value	0.66 [0.21, 2.11], 0.4832		0.85 [0.21, 3.51], 0.8206		0.76 [0.31, 1.87], 0.5511	
OR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4847		0.83 [0.17, 4.04], 0.8207		0.73 [0.26, 2.06], 0.5517	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5117		-0.02 [-0.16, 0.13], 0.8235		-0.03 [-0.15, 0.08], 0.5654	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	11/48 (22.9)	7/24 (29.2)	14/47 (29.8)	4/24 (16.7)	25/95 (26.3)	11/48 (22.9)
RR [95%-CI]; p-value	0.79 [0.35, 1.77], 0.5601		1.79 [0.66, 4.84], 0.2534		1.15 [0.62, 2.13], 0.6611	
OR [95%-CI]; p-value	0.72 [0.24, 2.19], 0.5637		2.12 [0.61, 7.35], 0.2293		1.20 [0.53, 2.71], 0.6583	
RD [95%-CI]; p-value	-0.06 [-0.28, 0.15], 0.5729		0.13 [-0.07, 0.33], 0.1947		0.03 [-0.11, 0.18], 0.6532	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_6_m_pt_adr_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.3360		0.0648		0.0083	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	12/18 (66.7)	5/5 (100.0)	16/32 (50.0)	4/5 (80.0)	28/50 (56.0)	9/10 (90.0)
RR [95%-CI]; p-value	0.73 [0.48, 1.12], 0.1480		0.63 [0.36, 1.09], 0.0992		0.62 [0.45, 0.86], 0.0038	
OR [95%-CI]; p-value	0.20 [0.01, 4.30], 0.2660		0.25 [0.03, 2.49], 0.2106		0.14 [0.02, 1.20], 0.0435	
RD [95%-CI]; p-value	-0.24 [-0.57, 0.08], 0.1428		-0.30 [-0.69, 0.09], 0.1327		-0.34 [-0.57, -0.11], 0.0040	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	80/108 (74.1)	51/63 (81.0)	66/98 (67.3)	37/61 (60.7)	146/206 (70.9)	88/124 (71.0)
RR [95%-CI]; p-value	0.92 [0.78, 1.08], 0.2877		1.11 [0.87, 1.42], 0.4018		1.00 [0.87, 1.15], 0.9855	
OR [95%-CI]; p-value	0.67 [0.31, 1.44], 0.3054		1.34 [0.69, 2.60], 0.3904		1.00 [0.61, 1.63], 0.9855	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.06], 0.2900		0.07 [-0.09, 0.22], 0.3938		-0.00 [-0.10, 0.10], 0.9855	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.8769		0.4316		0.8433	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	0/5 (0.0)	3/32 (9.4)	0/5 (0.0)	4/50 (8.0)	0/10 (0.0)
RR [95%-CI]; p-value	0.61 [0.02, 15.88], 0.7670		1.03 [0.06, 17.90], 0.9831		1.68 [0.10, 29.44], 0.7225	
OR [95%-CI]; p-value	0.59 [0.02, 20.24], 0.7666		1.03 [0.04, 23.92], 0.9831		1.74 [0.09, 35.58], 0.7162	
RD [95%-CI]; p-value	-0.04 [-0.30, 0.23], 0.7918		0.00 [-0.26, 0.26], 0.9830		0.03 [-0.12, 0.18], 0.6705	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	15/108 (13.9)	11/63 (17.5)	12/98 (12.2)	2/61 (3.3)	27/206 (13.1)	13/124 (10.5)
RR [95%-CI]; p-value	0.80 [0.39, 1.62], 0.5295		3.73 [0.87, 16.12], 0.0774		1.25 [0.67, 2.33], 0.4824	
OR [95%-CI]; p-value	0.76 [0.33, 1.78], 0.5304		4.12 [0.89, 19.07], 0.0524		1.29 [0.64, 2.60], 0.4795	
RD [95%-CI]; p-value	-0.04 [-0.15, 0.08], 0.5399		0.09 [0.01, 0.17], 0.0257		0.03 [-0.04, 0.10], 0.4686	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.0304		0.8160		0.0842	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	2/50 (4.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.34 [0.01, 9.06], 0.5224		0.20 [0.03, 1.26], 0.0862	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.32 [0.01, 10.94], 0.5095		0.17 [0.02, 1.36], 0.0641	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.06 [-0.31, 0.19], 0.6369		-0.16 [-0.41, 0.09], 0.2166	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	4/63 (6.3)	5/98 (5.1)	6/61 (9.8)	19/206 (9.2)	10/124 (8.1)
RR [95%-CI]; p-value	2.04 [0.70, 5.93], 0.1898		0.52 [0.17, 1.63], 0.2603		1.14 [0.55, 2.38], 0.7195	
OR [95%-CI]; p-value	2.20 [0.69, 6.99], 0.1740		0.49 [0.14, 1.69], 0.2527		1.16 [0.52, 2.58], 0.7188	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1380		-0.05 [-0.13, 0.04], 0.2834		0.01 [-0.05, 0.07], 0.7146	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.1782		0.8680		0.2373	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	5/32 (15.6)	1/5 (20.0)	8/50 (16.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.78 [0.11, 5.38], 0.8020		0.53 [0.17, 1.67], 0.2798	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.74 [0.07, 8.08], 0.8050		0.44 [0.09, 2.09], 0.2963	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.04 [-0.42, 0.33], 0.8179		-0.14 [-0.44, 0.16], 0.3630	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	22/108 (20.4)	10/63 (15.9)	12/98 (12.2)	8/61 (13.1)	34/206 (16.5)	18/124 (14.5)
RR [95%-CI]; p-value	1.28 [0.65, 2.53], 0.4720		0.93 [0.40, 2.15], 0.8721		1.14 [0.67, 1.92], 0.6324	
OR [95%-CI]; p-value	1.36 [0.60, 3.08], 0.4670		0.92 [0.35, 2.41], 0.8722		1.16 [0.63, 2.16], 0.6311	
RD [95%-CI]; p-value	0.04 [-0.07, 0.16], 0.4549		-0.01 [-0.12, 0.10], 0.8731		0.02 [-0.06, 0.10], 0.6265	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.7106		0.0720		0.3556	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	0/5 (0.0)	2/32 (6.3)	1/5 (20.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.61 [0.02, 15.88], 0.7670		0.31 [0.03, 2.84], 0.3018		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	0.59 [0.02, 20.24], 0.7666		0.27 [0.02, 3.65], 0.2949		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	-0.04 [-0.30, 0.23], 0.7918		-0.14 [-0.50, 0.22], 0.4547		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	10/108 (9.3)	5/63 (7.9)	8/98 (8.2)	1/61 (1.6)	18/206 (8.7)	6/124 (4.8)
RR [95%-CI]; p-value	1.17 [0.42, 3.26], 0.7687		4.98 [0.64, 38.84], 0.1256		1.81 [0.74, 4.43], 0.1964	
OR [95%-CI]; p-value	1.18 [0.39, 3.63], 0.7680		5.33 [0.65, 43.74], 0.0834		1.88 [0.73, 4.88], 0.1865	
RD [95%-CI]; p-value	0.01 [-0.07, 0.10], 0.7638		0.07 [0.00, 0.13], 0.0420		0.04 [-0.01, 0.09], 0.1568	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8493		0.2491		0.5048	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	0/5 (0.0)	1/32 (3.1)	1/5 (20.0)	2/50 (4.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.61 [0.02, 15.88], 0.7670		0.16 [0.01, 2.12], 0.1628		0.40 [0.04, 4.00], 0.4354	
OR [95%-CI]; p-value	0.59 [0.02, 20.24], 0.7666		0.13 [0.01, 2.49], 0.1207		0.38 [0.03, 4.59], 0.4268	
RD [95%-CI]; p-value	-0.04 [-0.30, 0.23], 0.7918		-0.17 [-0.52, 0.19], 0.3525		-0.06 [-0.25, 0.13], 0.5438	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	3/108 (2.8)	2/63 (3.2)	2/98 (2.0)	1/61 (1.6)	5/206 (2.4)	3/124 (2.4)
RR [95%-CI]; p-value	0.88 [0.15, 5.10], 0.8819		1.24 [0.12, 13.44], 0.8568		1.00 [0.24, 4.13], 0.9964	
OR [95%-CI]; p-value	0.87 [0.14, 5.36], 0.8819		1.25 [0.11, 14.09], 0.8564		1.00 [0.24, 4.27], 0.9964	
RD [95%-CI]; p-value	-0.00 [-0.06, 0.05], 0.8839		0.00 [-0.04, 0.05], 0.8528		0.00 [-0.03, 0.03], 0.9964	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.5065		0.5895		0.3603	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	2/50 (4.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		0.34 [0.01, 9.06], 0.5224		0.40 [0.04, 4.00], 0.4354	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		0.32 [0.01, 10.94], 0.5095		0.38 [0.03, 4.59], 0.4268	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		-0.06 [-0.31, 0.19], 0.6369		-0.06 [-0.25, 0.13], 0.5438	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	1/108 (0.9)	0/63 (0.0)	1/98 (1.0)	0/61 (0.0)	2/206 (1.0)	0/124 (0.0)
RR [95%-CI]; p-value	1.18 [0.04, 34.56], 0.9251		1.26 [0.04, 36.85], 0.8952		2.42 [0.11, 53.18], 0.5757	
OR [95%-CI]; p-value	1.18 [0.04, 35.60], 0.9250		1.26 [0.04, 38.06], 0.8949		2.43 [0.11, 54.35], 0.5627	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9235		0.00 [-0.03, 0.03], 0.8922		0.01 [-0.01, 0.02], 0.5213	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.2188		0.0084		0.0008	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	10/18 (55.6)	5/5 (100.0)	11/32 (34.4)	4/5 (80.0)	21/50 (42.0)	9/10 (90.0)
RR [95%-CI]; p-value	0.61 [0.37, 1.00], 0.0491		0.43 [0.22, 0.82], 0.0107		0.47 [0.32, 0.69], 0.0001	
OR [95%-CI]; p-value	0.13 [0.01, 2.65], 0.1310		0.13 [0.01, 1.32], 0.0533		0.08 [0.01, 0.68], 0.0056	
RD [95%-CI]; p-value	-0.35 [-0.69, -0.02], 0.0370		-0.46 [-0.84, -0.07], 0.0210		-0.48 [-0.71, -0.25], <0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	66/108 (61.1)	45/63 (71.4)	53/98 (54.1)	29/61 (47.5)	119/206 (57.8)	74/124 (59.7)
RR [95%-CI]; p-value	0.86 [0.69, 1.06], 0.1585		1.14 [0.83, 1.57], 0.4306		0.97 [0.80, 1.17], 0.7316	
OR [95%-CI]; p-value	0.63 [0.32, 1.23], 0.1727		1.30 [0.68, 2.47], 0.4223		0.92 [0.59, 1.45], 0.7330	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.04], 0.1619		0.07 [-0.09, 0.22], 0.4216		-0.02 [-0.13, 0.09], 0.7325	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.7955		0.3719		0.6748	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	7/18 (38.9)	2/5 (40.0)	10/32 (31.3)	2/5 (40.0)	17/50 (34.0)	4/10 (40.0)
RR [95%-CI]; p-value	0.97 [0.29, 3.29], 0.9639		0.78 [0.24, 2.57], 0.6844		0.85 [0.36, 1.99], 0.7084	
OR [95%-CI]; p-value	0.95 [0.13, 7.23], 0.9641		0.68 [0.10, 4.74], 0.6975		0.77 [0.19, 3.11], 0.7165	
RD [95%-CI]; p-value	-0.01 [-0.50, 0.47], 0.9642		-0.09 [-0.55, 0.37], 0.7083		-0.06 [-0.39, 0.27], 0.7222	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	38/108 (35.2)	27/63 (42.9)	34/98 (34.7)	15/61 (24.6)	72/206 (35.0)	42/124 (33.9)
RR [95%-CI]; p-value	0.82 [0.56, 1.20], 0.3130		1.41 [0.84, 2.37], 0.1916		1.03 [0.76, 1.40], 0.8419	
OR [95%-CI]; p-value	0.72 [0.38, 1.37], 0.3188		1.63 [0.80, 3.33], 0.1797		1.05 [0.66, 1.68], 0.8415	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.08], 0.3219		0.10 [-0.04, 0.24], 0.1672		0.01 [-0.09, 0.12], 0.8412	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.0304		0.8160		0.0842	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	2/50 (4.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.34 [0.01, 9.06], 0.5224		0.20 [0.03, 1.26], 0.0862	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.32 [0.01, 10.94], 0.5095		0.17 [0.02, 1.36], 0.0641	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.06 [-0.31, 0.19], 0.6369		-0.16 [-0.41, 0.09], 0.2166	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	4/63 (6.3)	5/98 (5.1)	6/61 (9.8)	19/206 (9.2)	10/124 (8.1)
RR [95%-CI]; p-value	2.04 [0.70, 5.93], 0.1898		0.52 [0.17, 1.63], 0.2603		1.14 [0.55, 2.38], 0.7195	
OR [95%-CI]; p-value	2.20 [0.69, 6.99], 0.1740		0.49 [0.14, 1.69], 0.2527		1.16 [0.52, 2.58], 0.7188	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1380		-0.05 [-0.13, 0.04], 0.2834		0.01 [-0.05, 0.07], 0.7146	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1647		0.8309		0.3196	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		1.03 [0.06, 17.90], 0.9831		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		1.03 [0.04, 23.92], 0.9831		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		0.00 [-0.26, 0.26], 0.9830		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	7/63 (11.1)	7/98 (7.1)	3/61 (4.9)	16/206 (7.8)	10/124 (8.1)
RR [95%-CI]; p-value	0.75 [0.29, 1.92], 0.5476		1.45 [0.39, 5.41], 0.5778		0.96 [0.45, 2.06], 0.9226	
OR [95%-CI]; p-value	0.73 [0.26, 2.06], 0.5474		1.49 [0.37, 5.98], 0.5742		0.96 [0.42, 2.19], 0.9226	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.5603		0.02 [-0.05, 0.10], 0.5581		-0.00 [-0.06, 0.06], 0.9229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6605		0.4194		0.9695	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	1/5 (20.0)	6/32 (18.8)	1/5 (20.0)	10/50 (20.0)	2/10 (20.0)
RR [95%-CI]; p-value	1.11 [0.16, 7.84], 0.9159		0.94 [0.14, 6.24], 0.9468		1.00 [0.26, 3.89], 1.0000	
OR [95%-CI]; p-value	1.14 [0.10, 13.34], 0.9151		0.92 [0.09, 9.82], 0.9471		1.00 [0.18, 5.46], 1.0000	
RD [95%-CI]; p-value	0.02 [-0.38, 0.42], 0.9132		-0.01 [-0.39, 0.36], 0.9480		0.00 [-0.27, 0.27], 1.0000	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	19/63 (30.2)	18/98 (18.4)	5/61 (8.2)	41/206 (19.9)	24/124 (19.4)
RR [95%-CI]; p-value	0.71 [0.42, 1.19], 0.1916		2.24 [0.88, 5.72], 0.0918		1.03 [0.65, 1.62], 0.9036	
OR [95%-CI]; p-value	0.63 [0.31, 1.27], 0.1940		2.52 [0.88, 7.19], 0.0762		1.04 [0.59, 1.82], 0.9035	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2053		0.10 [-0.00, 0.20], 0.0530		0.01 [-0.08, 0.09], 0.9032	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1588		0.1185		0.0384	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	2/5 (40.0)	4/50 (8.0)	4/10 (40.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.23 [0.05, 1.07], 0.0615		0.20 [0.06, 0.67], 0.0090	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.16 [0.02, 1.33], 0.0625		0.13 [0.03, 0.66], 0.0066	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.31 [-0.75, 0.13], 0.1736		-0.32 [-0.63, -0.01], 0.0450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	16/108 (14.8)	13/63 (20.6)	12/98 (12.2)	8/61 (13.1)	28/206 (13.6)	21/124 (16.9)
RR [95%-CI]; p-value	0.72 [0.37, 1.39], 0.3270		0.93 [0.40, 2.15], 0.8721		0.80 [0.48, 1.35], 0.4073	
OR [95%-CI]; p-value	0.67 [0.30, 1.50], 0.3279		0.92 [0.35, 2.41], 0.8722		0.77 [0.42, 1.43], 0.4081	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3431		-0.01 [-0.12, 0.10], 0.8731		-0.03 [-0.11, 0.05], 0.4181	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.6716		0.7312		0.4767	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	5/18 (27.8)	2/5 (40.0)	5/32 (15.6)	1/5 (20.0)	10/50 (20.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.69 [0.19, 2.57], 0.5844		0.78 [0.11, 5.38], 0.8020		0.67 [0.22, 2.00], 0.4688	
OR [95%-CI]; p-value	0.58 [0.07, 4.55], 0.5993		0.74 [0.07, 8.08], 0.8050		0.58 [0.13, 2.67], 0.4835	
RD [95%-CI]; p-value	-0.12 [-0.60, 0.35], 0.6153		-0.04 [-0.42, 0.33], 0.8179		-0.10 [-0.40, 0.20], 0.5203	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	29/108 (26.9)	18/63 (28.6)	25/98 (25.5)	14/61 (23.0)	54/206 (26.2)	32/124 (25.8)
RR [95%-CI]; p-value	0.94 [0.57, 1.55], 0.8075		1.11 [0.63, 1.97], 0.7166		1.02 [0.70, 1.48], 0.9350	
OR [95%-CI]; p-value	0.92 [0.46, 1.83], 0.8080		1.15 [0.54, 2.43], 0.7153		1.02 [0.61, 1.70], 0.9350	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.8089		0.03 [-0.11, 0.16], 0.7129		0.00 [-0.09, 0.10], 0.9349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8605		0.4487		0.8944	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	0/5 (0.0)	2/32 (6.3)	0/5 (0.0)	5/50 (10.0)	0/10 (0.0)
RR [95%-CI]; p-value	1.83 [0.11, 31.30], 0.6755		0.69 [0.04, 13.32], 0.8043		2.10 [0.12, 35.58], 0.6074	
OR [95%-CI]; p-value	2.00 [0.08, 47.16], 0.6623		0.67 [0.03, 17.03], 0.8051		2.22 [0.11, 44.05], 0.5914	
RD [95%-CI]; p-value	0.08 [-0.22, 0.37], 0.6154		-0.03 [-0.28, 0.23], 0.8268		0.05 [-0.10, 0.21], 0.5031	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	5/63 (7.9)	8/98 (8.2)	2/61 (3.3)	20/206 (9.7)	7/124 (5.6)
RR [95%-CI]; p-value	1.40 [0.52, 3.79], 0.5079		2.49 [0.55, 11.34], 0.2383		1.72 [0.75, 3.95], 0.2012	
OR [95%-CI]; p-value	1.45 [0.49, 4.33], 0.5033		2.62 [0.54, 12.78], 0.2173		1.80 [0.74, 4.38], 0.1921	
RD [95%-CI]; p-value	0.03 [-0.06, 0.12], 0.4858		0.05 [-0.02, 0.12], 0.1730		0.04 [-0.02, 0.10], 0.1646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5811		0.6751		0.9787	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	8/50 (16.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.56 [0.14, 2.20], 0.4032		1.38 [0.08, 22.55], 0.8234		0.80 [0.20, 3.22], 0.7535	
OR [95%-CI]; p-value	0.43 [0.05, 3.52], 0.4232		1.43 [0.06, 31.40], 0.8202		0.76 [0.14, 4.27], 0.7567	
RD [95%-CI]; p-value	-0.18 [-0.65, 0.29], 0.4589		0.03 [-0.23, 0.30], 0.8018		-0.04 [-0.31, 0.23], 0.7698	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	8/63 (12.7)	7/98 (7.1)	6/61 (9.8)	19/206 (9.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.88 [0.38, 2.02], 0.7551		0.73 [0.26, 2.06], 0.5475		0.82 [0.43, 1.57], 0.5441	
OR [95%-CI]; p-value	0.86 [0.33, 2.23], 0.7554		0.71 [0.23, 2.21], 0.5467		0.80 [0.38, 1.66], 0.5444	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.09], 0.7589		-0.03 [-0.12, 0.06], 0.5596		-0.02 [-0.09, 0.05], 0.5530	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0133		0.0628		0.0004	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	5/5 (100.0)	3/32 (9.4)	2/5 (40.0)	6/50 (12.0)	7/10 (70.0)
RR [95%-CI]; p-value	0.18 [0.06, 0.53], 0.0018		0.23 [0.05, 1.07], 0.0615		0.17 [0.07, 0.40], <0.0001	
OR [95%-CI]; p-value	0.02 [0.00, 0.47], 0.0013		0.16 [0.02, 1.33], 0.0625		0.06 [0.01, 0.29], <0.0001	
RD [95%-CI]; p-value	-0.74 [-1.00, -0.45], <0.0001		-0.31 [-0.75, 0.13], 0.1736		-0.58 [-0.88, -0.28], 0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	16/63 (25.4)	20/98 (20.4)	11/61 (18.0)	43/206 (20.9)	27/124 (21.8)
RR [95%-CI]; p-value	0.84 [0.48, 1.46], 0.5357		1.13 [0.58, 2.20], 0.7144		0.96 [0.63, 1.47], 0.8462	
OR [95%-CI]; p-value	0.79 [0.38, 1.65], 0.5376		1.17 [0.51, 2.64], 0.7131		0.95 [0.55, 1.63], 0.8463	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5437		0.02 [-0.10, 0.15], 0.7100		-0.01 [-0.10, 0.08], 0.8469	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4783		0.6825		0.9674	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	6/50 (12.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.28 [0.05, 1.51], 0.1376		1.38 [0.08, 22.55], 0.8234		0.60 [0.14, 2.56], 0.4896	
OR [95%-CI]; p-value	0.19 [0.02, 1.90], 0.1316		1.43 [0.06, 31.40], 0.8202		0.55 [0.09, 3.20], 0.4969	
RD [95%-CI]; p-value	-0.29 [-0.74, 0.16], 0.2116		0.03 [-0.23, 0.30], 0.8018		-0.08 [-0.34, 0.18], 0.5522	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	19/108 (17.6)	21/63 (33.3)	17/98 (17.3)	14/61 (23.0)	36/206 (17.5)	35/124 (28.2)
RR [95%-CI]; p-value	0.53 [0.31, 0.90], 0.0197		0.76 [0.40, 1.42], 0.3846		0.62 [0.41, 0.93], 0.0214	
OR [95%-CI]; p-value	0.43 [0.21, 0.88], 0.0190		0.70 [0.32, 1.56], 0.3858		0.54 [0.32, 0.92], 0.0214	
RD [95%-CI]; p-value	-0.16 [-0.29, -0.02], 0.0241		-0.06 [-0.19, 0.07], 0.3962		-0.11 [-0.20, -0.01], 0.0261	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.3894		0.1248		0.0753	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	1/5 (20.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.01, 3.48], 0.2271		0.16 [0.01, 2.12], 0.1628		0.10 [0.01, 1.00], 0.0500	
OR [95%-CI]; p-value	0.11 [0.00, 3.92], 0.1604		0.13 [0.01, 2.49], 0.1207		0.08 [0.01, 1.01], 0.0171	
RD [95%-CI]; p-value	-0.17 [-0.53, 0.19], 0.3441		-0.17 [-0.52, 0.19], 0.3525		-0.18 [-0.43, 0.07], 0.1598	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	12/63 (19.0)	15/98 (15.3)	7/61 (11.5)	27/206 (13.1)	19/124 (15.3)
RR [95%-CI]; p-value	0.58 [0.28, 1.22], 0.1519		1.33 [0.58, 3.08], 0.5006		0.86 [0.50, 1.47], 0.5729	
OR [95%-CI]; p-value	0.53 [0.22, 1.27], 0.1495		1.39 [0.53, 3.64], 0.4963		0.83 [0.44, 1.57], 0.5735	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1711		0.04 [-0.07, 0.15], 0.4834		-0.02 [-0.10, 0.06], 0.5795	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4290		0.6515		0.3238	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	4/32 (12.5)	1/5 (20.0)	7/50 (14.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.63 [0.09, 4.52], 0.6415		0.47 [0.14, 1.50], 0.2016	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.57 [0.05, 6.48], 0.6482		0.38 [0.08, 1.83], 0.2152	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.08 [-0.44, 0.29], 0.6902		-0.16 [-0.46, 0.14], 0.2957	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	10/63 (15.9)	10/98 (10.2)	6/61 (9.8)	24/206 (11.7)	16/124 (12.9)
RR [95%-CI]; p-value	0.82 [0.39, 1.73], 0.5965		1.04 [0.40, 2.71], 0.9402		0.90 [0.50, 1.63], 0.7353	
OR [95%-CI]; p-value	0.79 [0.33, 1.90], 0.5972		1.04 [0.36, 3.03], 0.9402		0.89 [0.45, 1.75], 0.7356	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.6049		0.00 [-0.09, 0.10], 0.9400		-0.01 [-0.09, 0.06], 0.7383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7803		0.0999		0.2848	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.16 [0.01, 2.12], 0.1628		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	NA		0.13 [0.01, 2.49], 0.1207		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	NA		-0.17 [-0.52, 0.19], 0.3525		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	9/63 (14.3)	13/98 (13.3)	5/61 (8.2)	21/206 (10.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.52 [0.21, 1.28], 0.1528		1.62 [0.61, 4.31], 0.3359		0.90 [0.48, 1.71], 0.7539	
OR [95%-CI]; p-value	0.48 [0.18, 1.32], 0.1471		1.71 [0.58, 5.07], 0.3267		0.89 [0.44, 1.83], 0.7541	
RD [95%-CI]; p-value	-0.07 [-0.17, 0.03], 0.1756		0.05 [-0.05, 0.15], 0.3016		-0.01 [-0.08, 0.06], 0.7567	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9729		0.0420		0.1170	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	2/5 (40.0)	4/50 (8.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.08 [0.01, 0.71], 0.0236		0.27 [0.07, 1.01], 0.0522	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.05 [0.00, 0.70], 0.0050		0.20 [0.04, 1.11], 0.0479	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.37 [-0.80, 0.06], 0.0956		-0.22 [-0.51, 0.07], 0.1422	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	11/108 (10.2)	8/63 (12.7)	8/98 (8.2)	5/61 (8.2)	19/206 (9.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.80 [0.34, 1.89], 0.6136		1.00 [0.34, 2.91], 0.9940		0.88 [0.45, 1.72], 0.7076	
OR [95%-CI]; p-value	0.78 [0.30, 2.05], 0.6139		1.00 [0.31, 3.20], 0.9940		0.87 [0.41, 1.82], 0.7078	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.6225		-0.00 [-0.09, 0.09], 0.9940		-0.01 [-0.08, 0.05], 0.7117	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.3.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4408		0.1922		0.8676	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		0.34 [0.01, 9.06], 0.5224		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		0.32 [0.01, 10.94], 0.5095		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		-0.06 [-0.31, 0.19], 0.6369		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	11/63 (17.5)	5/98 (5.1)	0/61 (0.0)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.21 [0.07, 0.64], 0.0058		6.28 [0.35, 112.87], 0.2128		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.18 [0.06, 0.60], 0.0022		6.56 [0.35, 122.22], 0.1485		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.14 [-0.24, -0.04], 0.0072		0.04 [-0.01, 0.09], 0.0863		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_3_m_pt_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.3.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5216		0.4760		0.8182	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.34 [0.01, 9.06], 0.5224		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.32 [0.01, 10.94], 0.5095		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.06 [-0.31, 0.19], 0.6369		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	3/108 (2.8)	8/63 (12.7)	6/98 (6.1)	3/61 (4.9)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.22 [0.06, 0.79], 0.0209		1.24 [0.32, 4.80], 0.7502		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.20 [0.05, 0.77], 0.0107		1.26 [0.30, 5.24], 0.7493		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.10 [-0.19, -0.01], 0.0269		0.01 [-0.06, 0.08], 0.7433		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_3_m_pt_ae10pct_dose.sas using SAS 9.4

Table 12.4.8.1.1.s7
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2864		0.4455		0.2523	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	0/32 (0.0)	0/5 (0.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		NA		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		NA		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		NA		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	5/108 (4.6)	2/63 (3.2)	4/98 (4.1)	3/61 (4.9)	9/206 (4.4)	5/124 (4.0)
RR [95%-CI]; p-value	1.46 [0.29, 7.30], 0.6460		0.83 [0.19, 3.58], 0.8027		1.08 [0.37, 3.16], 0.8832	
OR [95%-CI]; p-value	1.48 [0.28, 7.87], 0.6432		0.82 [0.18, 3.81], 0.8026		1.09 [0.36, 3.32], 0.8832	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.6270		-0.01 [-0.08, 0.06], 0.8065		0.00 [-0.04, 0.05], 0.8820	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_8_1_1_m_soc_sae5pct_dose.sas using SAS 9.4

Table 12.4.8.1.2.s7
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_8_1_2_m_pt_sae5pct_dose.sas using SAS 9.4

Table 12.4.5.1.1.s7
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_5_1_1_m_soc_aeg35pct_dose.sas using SAS 9.4

Table 12.4.5.1.2.s7
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_5_1_2_m_pt_aeg35pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1647		0.8309		0.3196	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		1.03 [0.06, 17.90], 0.9831		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		1.03 [0.04, 23.92], 0.9831		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		0.00 [-0.26, 0.26], 0.9830		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	7/63 (11.1)	7/98 (7.1)	3/61 (4.9)	16/206 (7.8)	10/124 (8.1)
RR [95%-CI]; p-value	0.75 [0.29, 1.92], 0.5476		1.45 [0.39, 5.41], 0.5778		0.96 [0.45, 2.06], 0.9226	
OR [95%-CI]; p-value	0.73 [0.26, 2.06], 0.5474		1.49 [0.37, 5.98], 0.5742		0.96 [0.42, 2.19], 0.9226	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.5603		0.02 [-0.05, 0.10], 0.5581		-0.00 [-0.06, 0.06], 0.9229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6605		0.4194		0.9695	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	1/5 (20.0)	6/32 (18.8)	1/5 (20.0)	10/50 (20.0)	2/10 (20.0)
RR [95%-CI]; p-value	1.11 [0.16, 7.84], 0.9159		0.94 [0.14, 6.24], 0.9468		1.00 [0.26, 3.89], 1.0000	
OR [95%-CI]; p-value	1.14 [0.10, 13.34], 0.9151		0.92 [0.09, 9.82], 0.9471		1.00 [0.18, 5.46], 1.0000	
RD [95%-CI]; p-value	0.02 [-0.38, 0.42], 0.9132		-0.01 [-0.39, 0.36], 0.9480		0.00 [-0.27, 0.27], 1.0000	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	19/63 (30.2)	18/98 (18.4)	5/61 (8.2)	41/206 (19.9)	24/124 (19.4)
RR [95%-CI]; p-value	0.71 [0.42, 1.19], 0.1916		2.24 [0.88, 5.72], 0.0918		1.03 [0.65, 1.62], 0.9036	
OR [95%-CI]; p-value	0.63 [0.31, 1.27], 0.1940		2.52 [0.88, 7.19], 0.0762		1.04 [0.59, 1.82], 0.9035	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2053		0.10 [-0.00, 0.20], 0.0530		0.01 [-0.08, 0.09], 0.9032	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1588		0.1185		0.0384	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	2/5 (40.0)	4/50 (8.0)	4/10 (40.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.23 [0.05, 1.07], 0.0615		0.20 [0.06, 0.67], 0.0090	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.16 [0.02, 1.33], 0.0625		0.13 [0.03, 0.66], 0.0066	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.31 [-0.75, 0.13], 0.1736		-0.32 [-0.63, -0.01], 0.0450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	16/108 (14.8)	13/63 (20.6)	12/98 (12.2)	8/61 (13.1)	28/206 (13.6)	21/124 (16.9)
RR [95%-CI]; p-value	0.72 [0.37, 1.39], 0.3270		0.93 [0.40, 2.15], 0.8721		0.80 [0.48, 1.35], 0.4073	
OR [95%-CI]; p-value	0.67 [0.30, 1.50], 0.3279		0.92 [0.35, 2.41], 0.8722		0.77 [0.42, 1.43], 0.4081	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3431		-0.01 [-0.12, 0.10], 0.8731		-0.03 [-0.11, 0.05], 0.4181	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.6716		0.7312		0.4767	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	5/18 (27.8)	2/5 (40.0)	5/32 (15.6)	1/5 (20.0)	10/50 (20.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.69 [0.19, 2.57], 0.5844		0.78 [0.11, 5.38], 0.8020		0.67 [0.22, 2.00], 0.4688	
OR [95%-CI]; p-value	0.58 [0.07, 4.55], 0.5993		0.74 [0.07, 8.08], 0.8050		0.58 [0.13, 2.67], 0.4835	
RD [95%-CI]; p-value	-0.12 [-0.60, 0.35], 0.6153		-0.04 [-0.42, 0.33], 0.8179		-0.10 [-0.40, 0.20], 0.5203	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	29/108 (26.9)	18/63 (28.6)	25/98 (25.5)	14/61 (23.0)	54/206 (26.2)	32/124 (25.8)
RR [95%-CI]; p-value	0.94 [0.57, 1.55], 0.8075		1.11 [0.63, 1.97], 0.7166		1.02 [0.70, 1.48], 0.9350	
OR [95%-CI]; p-value	0.92 [0.46, 1.83], 0.8080		1.15 [0.54, 2.43], 0.7153		1.02 [0.61, 1.70], 0.9350	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.8089		0.03 [-0.11, 0.16], 0.7129		0.00 [-0.09, 0.10], 0.9349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8605		0.4487		0.8944	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	0/5 (0.0)	2/32 (6.3)	0/5 (0.0)	5/50 (10.0)	0/10 (0.0)
RR [95%-CI]; p-value	1.83 [0.11, 31.30], 0.6755		0.69 [0.04, 13.32], 0.8043		2.10 [0.12, 35.58], 0.6074	
OR [95%-CI]; p-value	2.00 [0.08, 47.16], 0.6623		0.67 [0.03, 17.03], 0.8051		2.22 [0.11, 44.05], 0.5914	
RD [95%-CI]; p-value	0.08 [-0.22, 0.37], 0.6154		-0.03 [-0.28, 0.23], 0.8268		0.05 [-0.10, 0.21], 0.5031	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	5/63 (7.9)	8/98 (8.2)	2/61 (3.3)	20/206 (9.7)	7/124 (5.6)
RR [95%-CI]; p-value	1.40 [0.52, 3.79], 0.5079		2.49 [0.55, 11.34], 0.2383		1.72 [0.75, 3.95], 0.2012	
OR [95%-CI]; p-value	1.45 [0.49, 4.33], 0.5033		2.62 [0.54, 12.78], 0.2173		1.80 [0.74, 4.38], 0.1921	
RD [95%-CI]; p-value	0.03 [-0.06, 0.12], 0.4858		0.05 [-0.02, 0.12], 0.1730		0.04 [-0.02, 0.10], 0.1646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5811		0.6751		0.9787	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	8/50 (16.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.56 [0.14, 2.20], 0.4032		1.38 [0.08, 22.55], 0.8234		0.80 [0.20, 3.22], 0.7535	
OR [95%-CI]; p-value	0.43 [0.05, 3.52], 0.4232		1.43 [0.06, 31.40], 0.8202		0.76 [0.14, 4.27], 0.7567	
RD [95%-CI]; p-value	-0.18 [-0.65, 0.29], 0.4589		0.03 [-0.23, 0.30], 0.8018		-0.04 [-0.31, 0.23], 0.7698	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	8/63 (12.7)	7/98 (7.1)	6/61 (9.8)	19/206 (9.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.88 [0.38, 2.02], 0.7551		0.73 [0.26, 2.06], 0.5475		0.82 [0.43, 1.57], 0.5441	
OR [95%-CI]; p-value	0.86 [0.33, 2.23], 0.7554		0.71 [0.23, 2.21], 0.5467		0.80 [0.38, 1.66], 0.5444	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.09], 0.7589		-0.03 [-0.12, 0.06], 0.5596		-0.02 [-0.09, 0.05], 0.5530	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0133		0.0628		0.0004	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	5/5 (100.0)	3/32 (9.4)	2/5 (40.0)	6/50 (12.0)	7/10 (70.0)
RR [95%-CI]; p-value	0.18 [0.06, 0.53], 0.0018		0.23 [0.05, 1.07], 0.0615		0.17 [0.07, 0.40], <0.0001	
OR [95%-CI]; p-value	0.02 [0.00, 0.47], 0.0013		0.16 [0.02, 1.33], 0.0625		0.06 [0.01, 0.29], <0.0001	
RD [95%-CI]; p-value	-0.74 [-1.00, -0.45], <0.0001		-0.31 [-0.75, 0.13], 0.1736		-0.58 [-0.88, -0.28], 0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	16/63 (25.4)	20/98 (20.4)	11/61 (18.0)	43/206 (20.9)	27/124 (21.8)
RR [95%-CI]; p-value	0.84 [0.48, 1.46], 0.5357		1.13 [0.58, 2.20], 0.7144		0.96 [0.63, 1.47], 0.8462	
OR [95%-CI]; p-value	0.79 [0.38, 1.65], 0.5376		1.17 [0.51, 2.64], 0.7131		0.95 [0.55, 1.63], 0.8463	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5437		0.02 [-0.10, 0.15], 0.7100		-0.01 [-0.10, 0.08], 0.8469	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4783		0.6825		0.9674	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	6/50 (12.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.28 [0.05, 1.51], 0.1376		1.38 [0.08, 22.55], 0.8234		0.60 [0.14, 2.56], 0.4896	
OR [95%-CI]; p-value	0.19 [0.02, 1.90], 0.1316		1.43 [0.06, 31.40], 0.8202		0.55 [0.09, 3.20], 0.4969	
RD [95%-CI]; p-value	-0.29 [-0.74, 0.16], 0.2116		0.03 [-0.23, 0.30], 0.8018		-0.08 [-0.34, 0.18], 0.5522	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	19/108 (17.6)	21/63 (33.3)	17/98 (17.3)	14/61 (23.0)	36/206 (17.5)	35/124 (28.2)
RR [95%-CI]; p-value	0.53 [0.31, 0.90], 0.0197		0.76 [0.40, 1.42], 0.3846		0.62 [0.41, 0.93], 0.0214	
OR [95%-CI]; p-value	0.43 [0.21, 0.88], 0.0190		0.70 [0.32, 1.56], 0.3858		0.54 [0.32, 0.92], 0.0214	
RD [95%-CI]; p-value	-0.16 [-0.29, -0.02], 0.0241		-0.06 [-0.19, 0.07], 0.3962		-0.11 [-0.20, -0.01], 0.0261	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.3894		0.1248		0.0753	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	1/5 (20.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.01, 3.48], 0.2271		0.16 [0.01, 2.12], 0.1628		0.10 [0.01, 1.00], 0.0500	
OR [95%-CI]; p-value	0.11 [0.00, 3.92], 0.1604		0.13 [0.01, 2.49], 0.1207		0.08 [0.01, 1.01], 0.0171	
RD [95%-CI]; p-value	-0.17 [-0.53, 0.19], 0.3441		-0.17 [-0.52, 0.19], 0.3525		-0.18 [-0.43, 0.07], 0.1598	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	12/63 (19.0)	15/98 (15.3)	7/61 (11.5)	27/206 (13.1)	19/124 (15.3)
RR [95%-CI]; p-value	0.58 [0.28, 1.22], 0.1519		1.33 [0.58, 3.08], 0.5006		0.86 [0.50, 1.47], 0.5729	
OR [95%-CI]; p-value	0.53 [0.22, 1.27], 0.1495		1.39 [0.53, 3.64], 0.4963		0.83 [0.44, 1.57], 0.5735	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1711		0.04 [-0.07, 0.15], 0.4834		-0.02 [-0.10, 0.06], 0.5795	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.3214		0.1977		0.1002	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	1/32 (3.1)	1/5 (20.0)	2/50 (4.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		0.16 [0.01, 2.12], 0.1628		0.20 [0.03, 1.26], 0.0862	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		0.13 [0.01, 2.49], 0.1207		0.17 [0.02, 1.36], 0.0641	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		-0.17 [-0.52, 0.19], 0.3525		-0.16 [-0.41, 0.09], 0.2166	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	4/63 (6.3)	8/98 (8.2)	5/61 (8.2)	16/206 (7.8)	9/124 (7.3)
RR [95%-CI]; p-value	1.17 [0.37, 3.72], 0.7944		1.00 [0.34, 2.91], 0.9940		1.07 [0.49, 2.35], 0.8658	
OR [95%-CI]; p-value	1.18 [0.34, 4.09], 0.7939		1.00 [0.31, 3.20], 0.9940		1.08 [0.46, 2.51], 0.8656	
RD [95%-CI]; p-value	0.01 [-0.07, 0.09], 0.7900		-0.00 [-0.09, 0.09], 0.9940		0.01 [-0.05, 0.06], 0.8646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4290		0.6515		0.3238	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	4/32 (12.5)	1/5 (20.0)	7/50 (14.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.63 [0.09, 4.52], 0.6415		0.47 [0.14, 1.50], 0.2016	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.57 [0.05, 6.48], 0.6482		0.38 [0.08, 1.83], 0.2152	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.08 [-0.44, 0.29], 0.6902		-0.16 [-0.46, 0.14], 0.2957	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	10/63 (15.9)	10/98 (10.2)	6/61 (9.8)	24/206 (11.7)	16/124 (12.9)
RR [95%-CI]; p-value	0.82 [0.39, 1.73], 0.5965		1.04 [0.40, 2.71], 0.9402		0.90 [0.50, 1.63], 0.7353	
OR [95%-CI]; p-value	0.79 [0.33, 1.90], 0.5972		1.04 [0.36, 3.03], 0.9402		0.89 [0.45, 1.75], 0.7356	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.6049		0.00 [-0.09, 0.10], 0.9400		-0.01 [-0.09, 0.06], 0.7383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7803		0.0999		0.2848	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.16 [0.01, 2.12], 0.1628		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	NA		0.13 [0.01, 2.49], 0.1207		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	NA		-0.17 [-0.52, 0.19], 0.3525		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	9/63 (14.3)	13/98 (13.3)	5/61 (8.2)	21/206 (10.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.52 [0.21, 1.28], 0.1528		1.62 [0.61, 4.31], 0.3359		0.90 [0.48, 1.71], 0.7539	
OR [95%-CI]; p-value	0.48 [0.18, 1.32], 0.1471		1.71 [0.58, 5.07], 0.3267		0.89 [0.44, 1.83], 0.7541	
RD [95%-CI]; p-value	-0.07 [-0.17, 0.03], 0.1756		0.05 [-0.05, 0.15], 0.3016		-0.01 [-0.08, 0.06], 0.7567	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9729		0.0420		0.1170	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	2/5 (40.0)	4/50 (8.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.08 [0.01, 0.71], 0.0236		0.27 [0.07, 1.01], 0.0522	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.05 [0.00, 0.70], 0.0050		0.20 [0.04, 1.11], 0.0479	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.37 [-0.80, 0.06], 0.0956		-0.22 [-0.51, 0.07], 0.1422	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	11/108 (10.2)	8/63 (12.7)	8/98 (8.2)	5/61 (8.2)	19/206 (9.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.80 [0.34, 1.89], 0.6136		1.00 [0.34, 2.91], 0.9940		0.88 [0.45, 1.72], 0.7076	
OR [95%-CI]; p-value	0.78 [0.30, 2.05], 0.6139		1.00 [0.31, 3.20], 0.9940		0.87 [0.41, 1.82], 0.7078	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.6225		-0.00 [-0.09, 0.09], 0.9940		-0.01 [-0.08, 0.05], 0.7117	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.4.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4408		0.1922		0.8676	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		0.34 [0.01, 9.06], 0.5224		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		0.32 [0.01, 10.94], 0.5095		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		-0.06 [-0.31, 0.19], 0.6369		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	11/63 (17.5)	5/98 (5.1)	0/61 (0.0)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.21 [0.07, 0.64], 0.0058		6.28 [0.35, 112.87], 0.2128		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.18 [0.06, 0.60], 0.0022		6.56 [0.35, 122.22], 0.1485		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.14 [-0.24, -0.04], 0.0072		0.04 [-0.01, 0.09], 0.0863		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_4_m_pt_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.4.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5216		0.4760		0.8182	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.34 [0.01, 9.06], 0.5224		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.32 [0.01, 10.94], 0.5095		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.06 [-0.31, 0.19], 0.6369		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	3/108 (2.8)	8/63 (12.7)	6/98 (6.1)	3/61 (4.9)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.22 [0.06, 0.79], 0.0209		1.24 [0.32, 4.80], 0.7502		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.20 [0.05, 0.77], 0.0107		1.26 [0.30, 5.24], 0.7493		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.10 [-0.19, -0.01], 0.0269		0.01 [-0.06, 0.08], 0.7433		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_4_m_pt_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.4.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.6318		0.0772		0.0802	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	1/5 (20.0)	1/32 (3.1)	2/5 (40.0)	3/50 (6.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		0.08 [0.01, 0.71], 0.0236		0.20 [0.05, 0.85], 0.0295	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		0.05 [0.00, 0.70], 0.0050		0.15 [0.02, 0.89], 0.0209	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		-0.37 [-0.80, 0.06], 0.0956		-0.24 [-0.53, 0.05], 0.1067	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	7/108 (6.5)	4/63 (6.3)	5/98 (5.1)	4/61 (6.6)	12/206 (5.8)	8/124 (6.5)
RR [95%-CI]; p-value	1.02 [0.31, 3.35], 0.9729		0.78 [0.22, 2.79], 0.6997		0.90 [0.38, 2.15], 0.8173	
OR [95%-CI]; p-value	1.02 [0.29, 3.64], 0.9729		0.77 [0.20, 2.97], 0.6994		0.90 [0.36, 2.26], 0.8173	
RD [95%-CI]; p-value	0.00 [-0.07, 0.08], 0.9728		-0.01 [-0.09, 0.06], 0.7070		-0.01 [-0.06, 0.05], 0.8194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_4_m_pt_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.2108		0.8160		0.7232	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.34 [0.01, 9.06], 0.5224		0.80 [0.10, 6.43], 0.8337	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.32 [0.01, 10.94], 0.5095		0.78 [0.08, 7.84], 0.8345	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.06 [-0.31, 0.19], 0.6369		-0.02 [-0.22, 0.18], 0.8450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	1/63 (1.6)	5/98 (5.1)	6/61 (9.8)	14/206 (6.8)	7/124 (5.6)
RR [95%-CI]; p-value	5.25 [0.68, 40.48], 0.1116		0.52 [0.17, 1.63], 0.2603		1.20 [0.50, 2.90], 0.6792	
OR [95%-CI]; p-value	5.64 [0.70, 45.58], 0.0698		0.49 [0.14, 1.69], 0.2527		1.22 [0.48, 3.11], 0.6783	
RD [95%-CI]; p-value	0.07 [0.01, 0.13], 0.0291		-0.05 [-0.13, 0.04], 0.2834		0.01 [-0.04, 0.06], 0.6716	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5963		0.8163		0.6609	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	0/32 (0.0)	0/5 (0.0)	0/50 (0.0)	0/10 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	1/108 (0.9)	0/63 (0.0)	0/98 (0.0)	1/61 (1.6)	1/206 (0.5)	1/124 (0.8)
RR [95%-CI]; p-value	1.18 [0.04, 34.56], 0.9251		0.31 [0.01, 9.09], 0.4966		0.60 [0.04, 9.54], 0.7188	
OR [95%-CI]; p-value	1.18 [0.04, 35.60], 0.9250		0.31 [0.01, 9.26], 0.4717		0.60 [0.04, 9.68], 0.7159	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9235		-0.01 [-0.05, 0.02], 0.5241		-0.00 [-0.02, 0.02], 0.7321	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2430		0.7384		0.6752	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.34 [0.01, 9.06], 0.5224		0.80 [0.10, 6.43], 0.8337	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.32 [0.01, 10.94], 0.5095		0.78 [0.08, 7.84], 0.8345	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.06 [-0.31, 0.19], 0.6369		-0.02 [-0.22, 0.18], 0.8450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	1/63 (1.6)	5/98 (5.1)	5/61 (8.2)	13/206 (6.3)	6/124 (4.8)
RR [95%-CI]; p-value	4.67 [0.60, 36.45], 0.1419		0.62 [0.19, 2.06], 0.4378		1.30 [0.51, 3.34], 0.5803	
OR [95%-CI]; p-value	4.96 [0.61, 40.62], 0.1002		0.60 [0.17, 2.17], 0.4344		1.32 [0.49, 3.58], 0.5782	
RD [95%-CI]; p-value	0.06 [-0.00, 0.12], 0.0502		-0.03 [-0.11, 0.05], 0.4565		0.01 [-0.04, 0.07], 0.5662	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.1556		0.4409		0.0910	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	0/32 (0.0)	0/5 (0.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		NA		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		NA		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		NA		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	0/63 (0.0)	1/98 (1.0)	0/61 (0.0)	5/206 (2.4)	0/124 (0.0)
RR [95%-CI]; p-value	4.70 [0.25, 87.52], 0.2993		1.26 [0.04, 36.85], 0.8952		6.04 [0.33, 109.68], 0.2238	
OR [95%-CI]; p-value	4.85 [0.25, 93.20], 0.2486		1.26 [0.04, 38.06], 0.8949		6.17 [0.33, 113.89], 0.1631	
RD [95%-CI]; p-value	0.03 [-0.01, 0.07], 0.1707		0.00 [-0.03, 0.03], 0.8922		0.02 [-0.00, 0.04], 0.0949	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.6949		0.5243		0.8251	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	3/32 (9.4)	1/5 (20.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.47 [0.06, 3.67], 0.4705		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	NA		0.41 [0.03, 5.01], 0.4767		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	NA		-0.11 [-0.47, 0.26], 0.5682		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	10/108 (9.3)	9/63 (14.3)	8/98 (8.2)	5/61 (8.2)	18/206 (8.7)	14/124 (11.3)
RR [95%-CI]; p-value	0.65 [0.28, 1.51], 0.3146		1.00 [0.34, 2.91], 0.9940		0.77 [0.40, 1.50], 0.4480	
OR [95%-CI]; p-value	0.61 [0.23, 1.60], 0.3130		1.00 [0.31, 3.20], 0.9940		0.75 [0.36, 1.57], 0.4479	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3353		-0.00 [-0.09, 0.09], 0.9940		-0.03 [-0.09, 0.04], 0.4603	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5963		0.2874		0.2791	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	0/32 (0.0)	0/5 (0.0)	0/50 (0.0)	0/10 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	1/108 (0.9)	0/63 (0.0)	3/98 (3.1)	1/61 (1.6)	4/206 (1.9)	1/124 (0.8)
RR [95%-CI]; p-value	1.18 [0.04, 34.56], 0.9251		1.87 [0.20, 17.55], 0.5848		2.41 [0.27, 21.30], 0.4295	
OR [95%-CI]; p-value	1.18 [0.04, 35.60], 0.9250		1.89 [0.19, 18.64], 0.5777		2.44 [0.27, 22.04], 0.4135	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9235		0.01 [-0.03, 0.06], 0.5505		0.01 [-0.01, 0.04], 0.3648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7349		0.6980		0.9502	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	3/32 (9.4)	1/5 (20.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.47 [0.06, 3.67], 0.4705		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	NA		0.41 [0.03, 5.01], 0.4767		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	NA		-0.11 [-0.47, 0.26], 0.5682		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	9/63 (14.3)	6/98 (6.1)	5/61 (8.2)	15/206 (7.3)	14/124 (11.3)
RR [95%-CI]; p-value	0.58 [0.24, 1.39], 0.2247		0.75 [0.24, 2.34], 0.6168		0.64 [0.32, 1.29], 0.2151	
OR [95%-CI]; p-value	0.55 [0.20, 1.46], 0.2212		0.73 [0.21, 2.51], 0.6162		0.62 [0.29, 1.33], 0.2129	
RD [95%-CI]; p-value	-0.06 [-0.16, 0.04], 0.2476		-0.02 [-0.10, 0.06], 0.6268		-0.04 [-0.11, 0.03], 0.2342	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.2592		0.3228		0.2224	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	1/32 (3.1)	0/5 (0.0)	1/50 (2.0)	0/10 (0.0)
RR [95%-CI]; p-value	NA		0.34 [0.01, 9.06], 0.5224		0.42 [0.02, 11.72], 0.6095	
OR [95%-CI]; p-value	NA		0.32 [0.01, 10.94], 0.5095		0.41 [0.01, 13.02], 0.6008	
RD [95%-CI]; p-value	NA		-0.06 [-0.31, 0.19], 0.6369		-0.03 [-0.16, 0.11], 0.6874	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	0/63 (0.0)	4/98 (4.1)	1/61 (1.6)	8/206 (3.9)	1/124 (0.8)
RR [95%-CI]; p-value	4.70 [0.25, 87.52], 0.2993		2.49 [0.28, 21.76], 0.4095		4.82 [0.61, 38.04], 0.1361	
OR [95%-CI]; p-value	4.85 [0.25, 93.20], 0.2486		2.55 [0.28, 23.39], 0.3908		4.97 [0.61, 40.22], 0.0965	
RD [95%-CI]; p-value	0.03 [-0.01, 0.07], 0.1707		0.02 [-0.03, 0.07], 0.3432		0.03 [0.00, 0.06], 0.0496	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.6.s7
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.7816		0.3367		0.6848	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	4/32 (12.5)	1/5 (20.0)	7/50 (14.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.63 [0.09, 4.52], 0.6415		0.70 [0.17, 2.89], 0.6218	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.57 [0.05, 6.48], 0.6482		0.65 [0.11, 3.72], 0.6276	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.08 [-0.44, 0.29], 0.6902		-0.06 [-0.33, 0.21], 0.6583	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	18/108 (16.7)	17/63 (27.0)	20/98 (20.4)	7/61 (11.5)	38/206 (18.4)	24/124 (19.4)
RR [95%-CI]; p-value	0.62 [0.34, 1.11], 0.1068		1.78 [0.80, 3.95], 0.1580		0.95 [0.60, 1.51], 0.8377	
OR [95%-CI]; p-value	0.54 [0.26, 1.15], 0.1067		1.98 [0.78, 5.00], 0.1446		0.94 [0.53, 1.66], 0.8379	
RD [95%-CI]; p-value	-0.10 [-0.23, 0.03], 0.1204		0.09 [-0.02, 0.20], 0.1212		-0.01 [-0.10, 0.08], 0.8386	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_6_m_pt_adr_dose.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.1886		0.2714		0.0491	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	17/23 (73.9)	11/11 (100.0)	13/21 (61.9)	7/9 (77.8)	30/44 (68.2)	18/20 (90.0)
RR [95%-CI]; p-value	0.77 [0.59, 1.01], 0.0635		0.80 [0.49, 1.29], 0.3556		0.76 [0.59, 0.97], 0.0290	
OR [95%-CI]; p-value	0.13 [0.01, 2.54], 0.1237		0.46 [0.08, 2.81], 0.3980		0.24 [0.05, 1.17], 0.0617	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.00], 0.0472		-0.16 [-0.50, 0.18], 0.3629		-0.22 [-0.41, -0.03], 0.0247	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	84/118 (71.2)	45/61 (73.8)	78/123 (63.4)	37/63 (58.7)	162/241 (67.2)	82/124 (66.1)
RR [95%-CI]; p-value	0.96 [0.80, 1.17], 0.7110		1.08 [0.84, 1.38], 0.5421		1.02 [0.87, 1.19], 0.8348	
OR [95%-CI]; p-value	0.88 [0.44, 1.76], 0.7149		1.22 [0.65, 2.27], 0.5337		1.05 [0.66, 1.66], 0.8339	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7123		0.05 [-0.10, 0.20], 0.5361		0.01 [-0.09, 0.11], 0.8343	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.0442		0.2131		0.0164	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	4/11 (36.4)	3/21 (14.3)	1/9 (11.1)	4/44 (9.1)	5/20 (25.0)
RR [95%-CI]; p-value	0.12 [0.02, 0.95], 0.0443		1.29 [0.15, 10.76], 0.8166		0.36 [0.11, 1.21], 0.0996	
OR [95%-CI]; p-value	0.08 [0.01, 0.83], 0.0137		1.33 [0.12, 14.87], 0.8147		0.30 [0.07, 1.27], 0.0897	
RD [95%-CI]; p-value	-0.32 [-0.62, -0.02], 0.0342		0.03 [-0.22, 0.29], 0.8065		-0.16 [-0.37, 0.05], 0.1337	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	16/118 (13.6)	7/61 (11.5)	16/123 (13.0)	1/63 (1.6)	32/241 (13.3)	8/124 (6.5)
RR [95%-CI]; p-value	1.18 [0.51, 2.72], 0.6945		8.20 [1.11, 60.39], 0.0390		2.06 [0.98, 4.33], 0.0572	
OR [95%-CI]; p-value	1.21 [0.47, 3.12], 0.6929		9.27 [1.20, 71.61], 0.0105		2.22 [0.99, 4.98], 0.0480	
RD [95%-CI]; p-value	0.02 [-0.08, 0.12], 0.6861		0.11 [0.05, 0.18], 0.0008		0.07 [0.01, 0.13], 0.0279	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.4325		0.1586		0.8133	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	0/11 (0.0)	0/21 (0.0)	2/9 (22.2)	4/44 (9.1)	2/20 (10.0)
RR [95%-CI]; p-value	4.00 [0.23, 69.39], 0.3410		0.10 [0.01, 2.10], 0.1403		0.91 [0.18, 4.56], 0.9078	
OR [95%-CI]; p-value	4.63 [0.22, 96.08], 0.2835		0.08 [0.00, 2.07], 0.0677		0.90 [0.15, 5.37], 0.9079	
RD [95%-CI]; p-value	0.13 [-0.06, 0.33], 0.1891		-0.20 [-0.48, 0.08], 0.1622		-0.01 [-0.17, 0.15], 0.9094	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	6/61 (9.8)	10/123 (8.1)	5/63 (7.9)	24/241 (10.0)	11/124 (8.9)
RR [95%-CI]; p-value	1.21 [0.49, 2.98], 0.6847		1.02 [0.37, 2.87], 0.9634		1.12 [0.57, 2.22], 0.7389	
OR [95%-CI]; p-value	1.23 [0.45, 3.39], 0.6831		1.03 [0.34, 3.14], 0.9634		1.14 [0.54, 2.40], 0.7382	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6750		0.00 [-0.08, 0.08], 0.9633		0.01 [-0.05, 0.07], 0.7340	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.1584		0.1572		0.6028	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	9/23 (39.1)	1/11 (9.1)	1/21 (4.8)	2/9 (22.2)	10/44 (22.7)	3/20 (15.0)
RR [95%-CI]; p-value	4.30 [0.62, 29.86], 0.1397		0.21 [0.02, 2.07], 0.1835		1.52 [0.47, 4.92], 0.4890	
OR [95%-CI]; p-value	6.43 [0.70, 59.17], 0.0721		0.18 [0.01, 2.24], 0.1441		1.67 [0.40, 6.86], 0.4763	
RD [95%-CI]; p-value	0.30 [0.04, 0.56], 0.0246		-0.17 [-0.46, 0.11], 0.2323		0.08 [-0.12, 0.28], 0.4479	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	21/118 (17.8)	11/61 (18.0)	21/123 (17.1)	9/63 (14.3)	42/241 (17.4)	20/124 (16.1)
RR [95%-CI]; p-value	0.99 [0.51, 1.91], 0.9688		1.20 [0.58, 2.45], 0.6272		1.08 [0.66, 1.76], 0.7551	
OR [95%-CI]; p-value	0.98 [0.44, 2.20], 0.9688		1.24 [0.53, 2.88], 0.6247		1.10 [0.61, 1.97], 0.7544	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9689		0.03 [-0.08, 0.14], 0.6163		0.01 [-0.07, 0.09], 0.7520	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9368		0.6998		0.9320	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	7/23 (30.4)	2/11 (18.2)	1/21 (4.8)	0/9 (0.0)	8/44 (18.2)	2/20 (10.0)
RR [95%-CI]; p-value	1.67 [0.41, 6.77], 0.4700		0.90 [0.03, 24.71], 0.9527		1.82 [0.42, 7.80], 0.4211	
OR [95%-CI]; p-value	1.97 [0.34, 11.57], 0.4487		0.90 [0.03, 29.35], 0.9527		2.00 [0.38, 10.41], 0.4034	
RD [95%-CI]; p-value	0.12 [-0.17, 0.42], 0.4164		-0.01 [-0.17, 0.16], 0.9536		0.08 [-0.09, 0.26], 0.3567	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	9/118 (7.6)	3/61 (4.9)	14/123 (11.4)	4/63 (6.3)	23/241 (9.5)	7/124 (5.6)
RR [95%-CI]; p-value	1.55 [0.44, 5.52], 0.4981		1.79 [0.62, 5.22], 0.2845		1.69 [0.75, 3.83], 0.2083	
OR [95%-CI]; p-value	1.60 [0.42, 6.13], 0.4921		1.89 [0.60, 6.02], 0.2719		1.76 [0.73, 4.23], 0.1990	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.4632		0.05 [-0.03, 0.13], 0.2308		0.04 [-0.02, 0.09], 0.1648	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8835		0.6314		0.8399	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	2/44 (4.5)	0/20 (0.0)
RR [95%-CI]; p-value	2.00 [0.10, 40.86], 0.6525		0.44 [0.01, 20.66], 0.6771		1.86 [0.09, 39.52], 0.6895	
OR [95%-CI]; p-value	2.10 [0.09, 50.57], 0.6424		0.43 [0.01, 23.33], 0.6695		1.90 [0.08, 44.20], 0.6832	
RD [95%-CI]; p-value	0.04 [-0.12, 0.21], 0.6051		-0.03 [-0.19, 0.13], 0.7114		0.02 [-0.07, 0.11], 0.6494	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	2/61 (3.3)	7/123 (5.7)	3/63 (4.8)	13/241 (5.4)	5/124 (4.0)
RR [95%-CI]; p-value	1.55 [0.32, 7.46], 0.5839		1.20 [0.32, 4.46], 0.7910		1.34 [0.49, 3.67], 0.5717	
OR [95%-CI]; p-value	1.58 [0.31, 8.07], 0.5794		1.21 [0.30, 4.84], 0.7903		1.36 [0.47, 3.90], 0.5693	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5535		0.01 [-0.06, 0.08], 0.7847		0.01 [-0.03, 0.06], 0.5518	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.6123		0.5831		0.5722	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	0/23 (0.0)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	0/44 (0.0)	0/20 (0.0)
RR [95%-CI]; p-value	0.49 [0.01, 23.13], 0.7164		0.44 [0.01, 20.66], 0.6771		0.46 [0.01, 22.42], 0.6958	
OR [95%-CI]; p-value	0.48 [0.01, 25.73], 0.7112		0.43 [0.01, 23.33], 0.6695		0.45 [0.01, 23.73], 0.6889	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.11], 0.7407		-0.03 [-0.19, 0.13], 0.7114		-0.01 [-0.09, 0.06], 0.7261	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	3/118 (2.5)	1/61 (1.6)	3/123 (2.4)	1/63 (1.6)	6/241 (2.5)	2/124 (1.6)
RR [95%-CI]; p-value	1.55 [0.16, 14.60], 0.7013		1.54 [0.16, 14.47], 0.7074		1.54 [0.32, 7.54], 0.5915	
OR [95%-CI]; p-value	1.57 [0.16, 15.37], 0.6984		1.55 [0.16, 15.21], 0.7047		1.56 [0.31, 7.83], 0.5879	
RD [95%-CI]; p-value	0.01 [-0.03, 0.05], 0.6784		0.01 [-0.03, 0.05], 0.6852		0.01 [-0.02, 0.04], 0.5621	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.1348		0.6053		0.1567	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	11/23 (47.8)	9/11 (81.8)	12/21 (57.1)	6/9 (66.7)	23/44 (52.3)	15/20 (75.0)
RR [95%-CI]; p-value	0.58 [0.35, 0.97], 0.0390		0.86 [0.47, 1.55], 0.6099		0.70 [0.48, 1.02], 0.0620	
OR [95%-CI]; p-value	0.20 [0.04, 1.16], 0.0596		0.67 [0.13, 3.41], 0.6256		0.37 [0.11, 1.18], 0.0862	
RD [95%-CI]; p-value	-0.34 [-0.65, -0.03], 0.0295		-0.10 [-0.47, 0.28], 0.6174		-0.23 [-0.47, 0.01], 0.0639	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	71/118 (60.2)	41/61 (67.2)	58/123 (47.2)	29/63 (46.0)	129/241 (53.5)	70/124 (56.5)
RR [95%-CI]; p-value	0.90 [0.71, 1.13], 0.3426		1.02 [0.74, 1.42], 0.8849		0.95 [0.78, 1.15], 0.5915	
OR [95%-CI]; p-value	0.74 [0.38, 1.41], 0.3560		1.05 [0.57, 1.92], 0.8845		0.89 [0.57, 1.37], 0.5951	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3485		0.01 [-0.14, 0.16], 0.8845		-0.03 [-0.14, 0.08], 0.5943	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.4404		0.1185		0.5886	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	12/23 (52.2)	5/11 (45.5)	6/21 (28.6)	4/9 (44.4)	18/44 (40.9)	9/20 (45.0)
RR [95%-CI]; p-value	1.15 [0.54, 2.45], 0.7209		0.64 [0.24, 1.74], 0.3843		0.91 [0.50, 1.66], 0.7558	
OR [95%-CI]; p-value	1.31 [0.31, 5.53], 0.7139		0.50 [0.10, 2.53], 0.3980		0.85 [0.29, 2.46], 0.7587	
RD [95%-CI]; p-value	0.07 [-0.29, 0.43], 0.7131		-0.16 [-0.54, 0.22], 0.4102		-0.04 [-0.30, 0.22], 0.7596	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	38/118 (32.2)	24/61 (39.3)	43/123 (35.0)	14/63 (22.2)	81/241 (33.6)	38/124 (30.6)
RR [95%-CI]; p-value	0.82 [0.54, 1.23], 0.3348		1.57 [0.93, 2.65], 0.0883		1.10 [0.80, 1.51], 0.5701	
OR [95%-CI]; p-value	0.73 [0.39, 1.39], 0.3413		1.88 [0.93, 3.79], 0.0745		1.15 [0.72, 1.83], 0.5671	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3469		0.13 [-0.01, 0.26], 0.0602		0.03 [-0.07, 0.13], 0.5639	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.4325		0.1586		0.8133	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	0/11 (0.0)	0/21 (0.0)	2/9 (22.2)	4/44 (9.1)	2/20 (10.0)
RR [95%-CI]; p-value	4.00 [0.23, 69.39], 0.3410		0.10 [0.01, 2.10], 0.1403		0.91 [0.18, 4.56], 0.9078	
OR [95%-CI]; p-value	4.63 [0.22, 96.08], 0.2835		0.08 [0.00, 2.07], 0.0677		0.90 [0.15, 5.37], 0.9079	
RD [95%-CI]; p-value	0.13 [-0.06, 0.33], 0.1891		-0.20 [-0.48, 0.08], 0.1622		-0.01 [-0.17, 0.15], 0.9094	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	6/61 (9.8)	10/123 (8.1)	5/63 (7.9)	24/241 (10.0)	11/124 (8.9)
RR [95%-CI]; p-value	1.21 [0.49, 2.98], 0.6847		1.02 [0.37, 2.87], 0.9634		1.12 [0.57, 2.22], 0.7389	
OR [95%-CI]; p-value	1.23 [0.45, 3.39], 0.6831		1.03 [0.34, 3.14], 0.9634		1.14 [0.54, 2.40], 0.7382	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6750		0.00 [-0.08, 0.08], 0.9633		0.01 [-0.05, 0.07], 0.7340	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6827		0.8454		0.6000	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	1/21 (4.8)	0/9 (0.0)	4/44 (9.1)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.90 [0.03, 24.71], 0.9527		0.61 [0.15, 2.46], 0.4834	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.90 [0.03, 29.35], 0.9527		0.57 [0.11, 2.81], 0.4827	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.01 [-0.17, 0.16], 0.9536		-0.06 [-0.24, 0.12], 0.5154	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	6/61 (9.8)	10/123 (8.1)	4/63 (6.3)	18/241 (7.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.69 [0.25, 1.90], 0.4713		1.28 [0.42, 3.92], 0.6650		0.93 [0.44, 1.95], 0.8394	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4704		1.31 [0.39, 4.34], 0.6631		0.92 [0.41, 2.06], 0.8395	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.4932		0.02 [-0.06, 0.09], 0.6511		-0.01 [-0.06, 0.05], 0.8413	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8497		0.7577		0.8393	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	3/11 (27.3)	7/21 (33.3)	2/9 (22.2)	12/44 (27.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.80 [0.23, 2.75], 0.7196		1.50 [0.38, 5.87], 0.5601		1.09 [0.44, 2.68], 0.8496	
OR [95%-CI]; p-value	0.74 [0.14, 3.88], 0.7219		1.75 [0.29, 10.74], 0.5428		1.13 [0.34, 3.77], 0.8487	
RD [95%-CI]; p-value	-0.06 [-0.37, 0.26], 0.7286		0.11 [-0.23, 0.45], 0.5197		0.02 [-0.21, 0.25], 0.8470	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	23/118 (19.5)	17/61 (27.9)	19/123 (15.4)	5/63 (7.9)	42/241 (17.4)	22/124 (17.7)
RR [95%-CI]; p-value	0.70 [0.41, 1.21], 0.1989		1.95 [0.76, 4.97], 0.1637		0.98 [0.62, 1.57], 0.9403	
OR [95%-CI]; p-value	0.63 [0.30, 1.29], 0.2022		2.12 [0.75, 5.97], 0.1482		0.98 [0.55, 1.73], 0.9403	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2180		0.08 [-0.02, 0.17], 0.1111		-0.00 [-0.09, 0.08], 0.9405	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7284		0.0722		0.1454	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	0/21 (0.0)	3/9 (33.3)	2/44 (4.5)	4/20 (20.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.07 [0.00, 1.26], 0.0711		0.23 [0.05, 1.14], 0.0718	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.05 [0.00, 1.09], 0.0143		0.19 [0.03, 1.14], 0.0493	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.31 [-0.62, 0.00], 0.0533		-0.15 [-0.34, 0.03], 0.1030	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	17/118 (14.4)	14/61 (23.0)	17/123 (13.8)	8/63 (12.7)	34/241 (14.1)	22/124 (17.7)
RR [95%-CI]; p-value	0.63 [0.33, 1.19], 0.1515		1.09 [0.50, 2.38], 0.8322		0.80 [0.49, 1.30], 0.3598	
OR [95%-CI]; p-value	0.57 [0.26, 1.24], 0.1522		1.10 [0.45, 2.72], 0.8318		0.76 [0.42, 1.37], 0.3616	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1737		0.01 [-0.09, 0.11], 0.8298		-0.04 [-0.12, 0.04], 0.3752	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9811		0.4456		0.6764	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	8/23 (34.8)	4/11 (36.4)	5/21 (23.8)	1/9 (11.1)	13/44 (29.5)	5/20 (25.0)
RR [95%-CI]; p-value	0.96 [0.37, 2.50], 0.9278		2.14 [0.29, 15.83], 0.4551		1.18 [0.49, 2.87], 0.7116	
OR [95%-CI]; p-value	0.93 [0.21, 4.18], 0.9281		2.50 [0.25, 25.15], 0.4256		1.26 [0.38, 4.18], 0.7077	
RD [95%-CI]; p-value	-0.02 [-0.36, 0.33], 0.9283		0.13 [-0.15, 0.40], 0.3645		0.05 [-0.19, 0.28], 0.7019	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	30/118 (25.4)	16/61 (26.2)	28/123 (22.8)	15/63 (23.8)	58/241 (24.1)	31/124 (25.0)
RR [95%-CI]; p-value	0.97 [0.58, 1.63], 0.9068		0.96 [0.55, 1.66], 0.8726		0.96 [0.66, 1.41], 0.8437	
OR [95%-CI]; p-value	0.96 [0.47, 1.94], 0.9069		0.94 [0.46, 1.93], 0.8729		0.95 [0.58, 1.57], 0.8440	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.13], 0.9072		-0.01 [-0.14, 0.12], 0.8735		-0.01 [-0.10, 0.08], 0.8447	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8496		0.9217		0.7953	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	1/11 (9.1)	2/21 (9.5)	0/9 (0.0)	5/44 (11.4)	1/20 (5.0)
RR [95%-CI]; p-value	1.43 [0.17, 12.27], 0.7416		1.81 [0.09, 36.44], 0.6987		2.27 [0.28, 18.21], 0.4394	
OR [95%-CI]; p-value	1.50 [0.14, 16.32], 0.7379		1.89 [0.08, 46.43], 0.6912		2.44 [0.27, 22.34], 0.4182	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7231		0.04 [-0.15, 0.23], 0.6595		0.06 [-0.07, 0.20], 0.3514	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	4/61 (6.6)	9/123 (7.3)	3/63 (4.8)	23/241 (9.5)	7/124 (5.6)
RR [95%-CI]; p-value	1.81 [0.62, 5.26], 0.2762		1.54 [0.43, 5.48], 0.5077		1.69 [0.75, 3.83], 0.2083	
OR [95%-CI]; p-value	1.92 [0.60, 6.10], 0.2631		1.58 [0.41, 6.05], 0.5020		1.76 [0.73, 4.23], 0.1990	
RD [95%-CI]; p-value	0.05 [-0.03, 0.14], 0.2223		0.03 [-0.04, 0.10], 0.4736		0.04 [-0.02, 0.09], 0.1648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2630		0.0899		0.7859	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	7/44 (15.9)	4/20 (20.0)
RR [95%-CI]; p-value	2.39 [0.32, 18.08], 0.3983		0.29 [0.06, 1.43], 0.1272		0.80 [0.26, 2.41], 0.6859	
OR [95%-CI]; p-value	2.78 [0.28, 27.21], 0.3654		0.21 [0.03, 1.57], 0.1088		0.76 [0.19, 2.95], 0.6876	
RD [95%-CI]; p-value	0.13 [-0.11, 0.37], 0.3003		-0.24 [-0.57, 0.09], 0.1606		-0.04 [-0.25, 0.17], 0.6970	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	12/118 (10.2)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	24/241 (10.0)	13/124 (10.5)
RR [95%-CI]; p-value	0.69 [0.31, 1.54], 0.3662		1.54 [0.52, 4.57], 0.4399		0.95 [0.50, 1.80], 0.8747	
OR [95%-CI]; p-value	0.65 [0.26, 1.65], 0.3663		1.59 [0.49, 5.16], 0.4329		0.94 [0.46, 1.93], 0.8748	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.06], 0.3893		0.03 [-0.05, 0.11], 0.4030		-0.01 [-0.07, 0.06], 0.8757	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6851		0.7812		0.9433	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	2/11 (18.2)	3/21 (14.3)	1/9 (11.1)	5/44 (11.4)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.08, 2.96], 0.4279		1.29 [0.15, 10.76], 0.8166		0.76 [0.20, 2.86], 0.6825	
OR [95%-CI]; p-value	0.43 [0.05, 3.53], 0.4219		1.33 [0.12, 14.87], 0.8147		0.73 [0.16, 3.39], 0.6835	
RD [95%-CI]; p-value	-0.09 [-0.35, 0.16], 0.4666		0.03 [-0.22, 0.29], 0.8065		-0.04 [-0.22, 0.15], 0.6960	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	26/118 (22.0)	19/61 (31.1)	22/123 (17.9)	12/63 (19.0)	48/241 (19.9)	31/124 (25.0)
RR [95%-CI]; p-value	0.71 [0.43, 1.17], 0.1786		0.94 [0.50, 1.77], 0.8459		0.80 [0.54, 1.18], 0.2609	
OR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1828		0.93 [0.42, 2.02], 0.8462		0.75 [0.45, 1.25], 0.2641	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.1962		-0.01 [-0.13, 0.11], 0.8474		-0.05 [-0.14, 0.04], 0.2756	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5187		0.1364		0.1410	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	5/11 (45.5)	3/21 (14.3)	4/9 (44.4)	7/44 (15.9)	9/20 (45.0)
RR [95%-CI]; p-value	0.38 [0.13, 1.15], 0.0872		0.32 [0.09, 1.15], 0.0815		0.35 [0.15, 0.81], 0.0146	
OR [95%-CI]; p-value	0.25 [0.05, 1.26], 0.0827		0.21 [0.03, 1.25], 0.0735		0.23 [0.07, 0.76], 0.0127	
RD [95%-CI]; p-value	-0.28 [-0.61, 0.05], 0.0981		-0.30 [-0.66, 0.06], 0.0982		-0.29 [-0.53, -0.05], 0.0191	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	20/118 (16.9)	18/61 (29.5)	19/123 (15.4)	10/63 (15.9)	39/241 (16.2)	28/124 (22.6)
RR [95%-CI]; p-value	0.57 [0.33, 1.00], 0.0509		0.97 [0.48, 1.97], 0.9396		0.72 [0.46, 1.11], 0.1329	
OR [95%-CI]; p-value	0.49 [0.23, 1.01], 0.0515		0.97 [0.42, 2.23], 0.9396		0.66 [0.38, 1.14], 0.1348	
RD [95%-CI]; p-value	-0.13 [-0.26, 0.01], 0.0641		-0.00 [-0.11, 0.11], 0.9398		-0.06 [-0.15, 0.02], 0.1497	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9948		0.0501		0.2189	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	3/44 (6.8)	4/20 (20.0)
RR [95%-CI]; p-value	0.48 [0.03, 6.96], 0.5892		0.29 [0.06, 1.43], 0.1272		0.34 [0.08, 1.38], 0.1321	
OR [95%-CI]; p-value	0.45 [0.03, 8.02], 0.5824		0.21 [0.03, 1.57], 0.1088		0.29 [0.06, 1.46], 0.1173	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6232		-0.24 [-0.57, 0.09], 0.1606		-0.13 [-0.32, 0.06], 0.1750	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	11/118 (9.3)	12/61 (19.7)	18/123 (14.6)	5/63 (7.9)	29/241 (12.0)	17/124 (13.7)
RR [95%-CI]; p-value	0.47 [0.22, 1.01], 0.0533		1.84 [0.72, 4.74], 0.2035		0.88 [0.50, 1.53], 0.6469	
OR [95%-CI]; p-value	0.42 [0.17, 1.02], 0.0498		1.99 [0.70, 5.63], 0.1891		0.86 [0.45, 1.64], 0.6476	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0719		0.07 [-0.02, 0.16], 0.1510		-0.02 [-0.09, 0.06], 0.6533	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4770		0.3543		0.3166	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	5/21 (23.8)	3/9 (33.3)	8/44 (18.2)	6/20 (30.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.71 [0.22, 2.37], 0.5825		0.61 [0.24, 1.52], 0.2845	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.63 [0.11, 3.46], 0.5888		0.52 [0.15, 1.77], 0.2891	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.10 [-0.45, 0.26], 0.6019		-0.12 [-0.35, 0.11], 0.3158	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	15/118 (12.7)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	27/241 (11.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.86 [0.40, 1.85], 0.7032		1.54 [0.52, 4.57], 0.4399		1.07 [0.57, 2.00], 0.8352	
OR [95%-CI]; p-value	0.84 [0.35, 2.05], 0.7039		1.59 [0.49, 5.16], 0.4329		1.08 [0.53, 2.17], 0.8349	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7094		0.03 [-0.05, 0.11], 0.4030		0.01 [-0.06, 0.07], 0.8334	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4758		0.0241		0.0222	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	2/11 (18.2)	0/21 (0.0)	3/9 (33.3)	1/44 (2.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.24 [0.02, 2.36], 0.2208		0.07 [0.00, 1.26], 0.0711		0.09 [0.01, 0.73], 0.0239	
OR [95%-CI]; p-value	0.20 [0.02, 2.55], 0.1834		0.05 [0.00, 1.09], 0.0143		0.07 [0.01, 0.65], 0.0038	
RD [95%-CI]; p-value	-0.14 [-0.38, 0.10], 0.2639		-0.31 [-0.62, 0.00], 0.0533		-0.23 [-0.42, -0.03], 0.0222	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	7/61 (11.5)	15/123 (12.2)	3/63 (4.8)	23/241 (9.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.59 [0.22, 1.55], 0.2857		2.56 [0.77, 8.52], 0.1251		1.18 [0.58, 2.41], 0.6421	
OR [95%-CI]; p-value	0.56 [0.19, 1.63], 0.2825		2.78 [0.77, 9.98], 0.1046		1.20 [0.55, 2.61], 0.6407	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.04], 0.3169		0.07 [-0.00, 0.15], 0.0623		0.01 [-0.05, 0.08], 0.6324	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9167		0.6331		0.8171	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	1/21 (4.8)	1/9 (11.1)	3/44 (6.8)	2/20 (10.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.43 [0.03, 6.12], 0.5324		0.68 [0.12, 3.77], 0.6606	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.40 [0.02, 7.20], 0.5229		0.66 [0.10, 4.29], 0.6602	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.06 [-0.29, 0.16], 0.5796		-0.03 [-0.18, 0.12], 0.6798	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	13/118 (11.0)	8/61 (13.1)	10/123 (8.1)	6/63 (9.5)	23/241 (9.5)	14/124 (11.3)
RR [95%-CI]; p-value	0.84 [0.37, 1.92], 0.6787		0.85 [0.33, 2.24], 0.7481		0.85 [0.45, 1.58], 0.5999	
OR [95%-CI]; p-value	0.82 [0.32, 2.10], 0.6793		0.84 [0.29, 2.43], 0.7483		0.83 [0.41, 1.67], 0.6005	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.08], 0.6863		-0.01 [-0.10, 0.07], 0.7538		-0.02 [-0.08, 0.05], 0.6090	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.3.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3428		0.6996		0.5170	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	0/23 (0.0)	3/11 (27.3)	2/21 (9.5)	0/9 (0.0)	2/44 (4.5)	3/20 (15.0)
RR [95%-CI]; p-value	0.08 [0.00, 1.43], 0.0855		1.81 [0.09, 36.44], 0.6987		0.30 [0.05, 1.67], 0.1710	
OR [95%-CI]; p-value	0.06 [0.00, 1.29], 0.0226		1.89 [0.08, 46.43], 0.6912		0.27 [0.04, 1.76], 0.1486	
RD [95%-CI]; p-value	-0.25 [-0.52, 0.02], 0.0675		0.04 [-0.15, 0.23], 0.6595		-0.10 [-0.27, 0.06], 0.2230	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	9/61 (14.8)	4/123 (3.3)	0/63 (0.0)	10/241 (4.1)	9/124 (7.3)
RR [95%-CI]; p-value	0.34 [0.13, 0.92], 0.0342		4.13 [0.22, 76.91], 0.3418		0.57 [0.24, 1.37], 0.2099	
OR [95%-CI]; p-value	0.31 [0.10, 0.92], 0.0269		4.24 [0.22, 81.39], 0.2986		0.55 [0.22, 1.40], 0.2054	
RD [95%-CI]; p-value	-0.10 [-0.19, 0.00], 0.0517		0.02 [-0.01, 0.06], 0.2054		-0.03 [-0.08, 0.02], 0.2426	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_3_m_pt_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.3.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2083		0.7775		0.2135	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	0/11 (0.0)	2/21 (9.5)	1/9 (11.1)	4/44 (9.1)	1/20 (5.0)
RR [95%-CI]; p-value	2.00 [0.10, 40.86], 0.6525		0.86 [0.09, 8.30], 0.8941		1.82 [0.22, 15.25], 0.5816	
OR [95%-CI]; p-value	2.10 [0.09, 50.57], 0.6424		0.84 [0.07, 10.66], 0.8943		1.90 [0.20, 18.18], 0.5719	
RD [95%-CI]; p-value	0.04 [-0.12, 0.21], 0.6051		-0.02 [-0.26, 0.22], 0.8971		0.04 [-0.09, 0.17], 0.5305	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	5/118 (4.2)	10/61 (16.4)	5/123 (4.1)	2/63 (3.2)	10/241 (4.1)	12/124 (9.7)
RR [95%-CI]; p-value	0.26 [0.09, 0.72], 0.0099		1.28 [0.26, 6.42], 0.7636		0.43 [0.19, 0.96], 0.0406	
OR [95%-CI]; p-value	0.23 [0.07, 0.69], 0.0054		1.29 [0.24, 6.86], 0.7627		0.40 [0.17, 0.96], 0.0356	
RD [95%-CI]; p-value	-0.12 [-0.22, -0.02], 0.0169		0.01 [-0.05, 0.06], 0.7536		-0.06 [-0.11, 0.00], 0.0609	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_3_m_pt_ae10pct_vitd.sas using SAS 9.4

Table 12.4.8.1.1.s8
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9181		0.3342		0.5003	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	1/9 (11.1)	1/44 (2.3)	1/20 (5.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		0.21 [0.01, 5.70], 0.3536		0.45 [0.03, 6.91], 0.5701	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		0.19 [0.01, 6.25], 0.3062		0.44 [0.03, 7.44], 0.5611	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		-0.09 [-0.30, 0.13], 0.4231		-0.03 [-0.13, 0.08], 0.6113	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	7/118 (5.9)	3/61 (4.9)	5/123 (4.1)	2/63 (3.2)	12/241 (5.0)	5/124 (4.0)
RR [95%-CI]; p-value	1.21 [0.32, 4.50], 0.7802		1.28 [0.26, 6.42], 0.7636		1.23 [0.45, 3.43], 0.6854	
OR [95%-CI]; p-value	1.22 [0.30, 4.89], 0.7795		1.29 [0.24, 6.86], 0.7627		1.25 [0.43, 3.62], 0.6843	
RD [95%-CI]; p-value	0.01 [-0.06, 0.08], 0.7733		0.01 [-0.05, 0.06], 0.7536		0.01 [-0.03, 0.05], 0.6745	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_8_1_1_m_soc_sae5pct_vitd.sas using SAS 9.4

Table 12.4.8.1.2.s8
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_8_1_2_m_pt_sae5pct_vitd.sas using SAS 9.4

Table 12.4.5.1.1.s8
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_5_1_1_m_soc_aeg35pct_vitd.sas using SAS 9.4

Table 12.4.5.1.2.s8
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_5_1_2_m_pt_aeg35pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6827		0.8454		0.6000	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	1/21 (4.8)	0/9 (0.0)	4/44 (9.1)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.90 [0.03, 24.71], 0.9527		0.61 [0.15, 2.46], 0.4834	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.90 [0.03, 29.35], 0.9527		0.57 [0.11, 2.81], 0.4827	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.01 [-0.17, 0.16], 0.9536		-0.06 [-0.24, 0.12], 0.5154	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	6/61 (9.8)	10/123 (8.1)	4/63 (6.3)	18/241 (7.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.69 [0.25, 1.90], 0.4713		1.28 [0.42, 3.92], 0.6650		0.93 [0.44, 1.95], 0.8394	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4704		1.31 [0.39, 4.34], 0.6631		0.92 [0.41, 2.06], 0.8395	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.4932		0.02 [-0.06, 0.09], 0.6511		-0.01 [-0.06, 0.05], 0.8413	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8497		0.7577		0.8393	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	3/11 (27.3)	7/21 (33.3)	2/9 (22.2)	12/44 (27.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.80 [0.23, 2.75], 0.7196		1.50 [0.38, 5.87], 0.5601		1.09 [0.44, 2.68], 0.8496	
OR [95%-CI]; p-value	0.74 [0.14, 3.88], 0.7219		1.75 [0.29, 10.74], 0.5428		1.13 [0.34, 3.77], 0.8487	
RD [95%-CI]; p-value	-0.06 [-0.37, 0.26], 0.7286		0.11 [-0.23, 0.45], 0.5197		0.02 [-0.21, 0.25], 0.8470	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	23/118 (19.5)	17/61 (27.9)	19/123 (15.4)	5/63 (7.9)	42/241 (17.4)	22/124 (17.7)
RR [95%-CI]; p-value	0.70 [0.41, 1.21], 0.1989		1.95 [0.76, 4.97], 0.1637		0.98 [0.62, 1.57], 0.9403	
OR [95%-CI]; p-value	0.63 [0.30, 1.29], 0.2022		2.12 [0.75, 5.97], 0.1482		0.98 [0.55, 1.73], 0.9403	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2180		0.08 [-0.02, 0.17], 0.1111		-0.00 [-0.09, 0.08], 0.9405	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7284		0.0722		0.1454	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	0/21 (0.0)	3/9 (33.3)	2/44 (4.5)	4/20 (20.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.07 [0.00, 1.26], 0.0711		0.23 [0.05, 1.14], 0.0718	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.05 [0.00, 1.09], 0.0143		0.19 [0.03, 1.14], 0.0493	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.31 [-0.62, 0.00], 0.0533		-0.15 [-0.34, 0.03], 0.1030	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	17/118 (14.4)	14/61 (23.0)	17/123 (13.8)	8/63 (12.7)	34/241 (14.1)	22/124 (17.7)
RR [95%-CI]; p-value	0.63 [0.33, 1.19], 0.1515		1.09 [0.50, 2.38], 0.8322		0.80 [0.49, 1.30], 0.3598	
OR [95%-CI]; p-value	0.57 [0.26, 1.24], 0.1522		1.10 [0.45, 2.72], 0.8318		0.76 [0.42, 1.37], 0.3616	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1737		0.01 [-0.09, 0.11], 0.8298		-0.04 [-0.12, 0.04], 0.3752	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9811		0.4456		0.6764	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	8/23 (34.8)	4/11 (36.4)	5/21 (23.8)	1/9 (11.1)	13/44 (29.5)	5/20 (25.0)
RR [95%-CI]; p-value	0.96 [0.37, 2.50], 0.9278		2.14 [0.29, 15.83], 0.4551		1.18 [0.49, 2.87], 0.7116	
OR [95%-CI]; p-value	0.93 [0.21, 4.18], 0.9281		2.50 [0.25, 25.15], 0.4256		1.26 [0.38, 4.18], 0.7077	
RD [95%-CI]; p-value	-0.02 [-0.36, 0.33], 0.9283		0.13 [-0.15, 0.40], 0.3645		0.05 [-0.19, 0.28], 0.7019	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	30/118 (25.4)	16/61 (26.2)	28/123 (22.8)	15/63 (23.8)	58/241 (24.1)	31/124 (25.0)
RR [95%-CI]; p-value	0.97 [0.58, 1.63], 0.9068		0.96 [0.55, 1.66], 0.8726		0.96 [0.66, 1.41], 0.8437	
OR [95%-CI]; p-value	0.96 [0.47, 1.94], 0.9069		0.94 [0.46, 1.93], 0.8729		0.95 [0.58, 1.57], 0.8440	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.13], 0.9072		-0.01 [-0.14, 0.12], 0.8735		-0.01 [-0.10, 0.08], 0.8447	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8496		0.9217		0.7953	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	1/11 (9.1)	2/21 (9.5)	0/9 (0.0)	5/44 (11.4)	1/20 (5.0)
RR [95%-CI]; p-value	1.43 [0.17, 12.27], 0.7416		1.81 [0.09, 36.44], 0.6987		2.27 [0.28, 18.21], 0.4394	
OR [95%-CI]; p-value	1.50 [0.14, 16.32], 0.7379		1.89 [0.08, 46.43], 0.6912		2.44 [0.27, 22.34], 0.4182	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7231		0.04 [-0.15, 0.23], 0.6595		0.06 [-0.07, 0.20], 0.3514	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	4/61 (6.6)	9/123 (7.3)	3/63 (4.8)	23/241 (9.5)	7/124 (5.6)
RR [95%-CI]; p-value	1.81 [0.62, 5.26], 0.2762		1.54 [0.43, 5.48], 0.5077		1.69 [0.75, 3.83], 0.2083	
OR [95%-CI]; p-value	1.92 [0.60, 6.10], 0.2631		1.58 [0.41, 6.05], 0.5020		1.76 [0.73, 4.23], 0.1990	
RD [95%-CI]; p-value	0.05 [-0.03, 0.14], 0.2223		0.03 [-0.04, 0.10], 0.4736		0.04 [-0.02, 0.09], 0.1648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2630		0.0899		0.7859	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	7/44 (15.9)	4/20 (20.0)
RR [95%-CI]; p-value	2.39 [0.32, 18.08], 0.3983		0.29 [0.06, 1.43], 0.1272		0.80 [0.26, 2.41], 0.6859	
OR [95%-CI]; p-value	2.78 [0.28, 27.21], 0.3654		0.21 [0.03, 1.57], 0.1088		0.76 [0.19, 2.95], 0.6876	
RD [95%-CI]; p-value	0.13 [-0.11, 0.37], 0.3003		-0.24 [-0.57, 0.09], 0.1606		-0.04 [-0.25, 0.17], 0.6970	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	12/118 (10.2)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	24/241 (10.0)	13/124 (10.5)
RR [95%-CI]; p-value	0.69 [0.31, 1.54], 0.3662		1.54 [0.52, 4.57], 0.4399		0.95 [0.50, 1.80], 0.8747	
OR [95%-CI]; p-value	0.65 [0.26, 1.65], 0.3663		1.59 [0.49, 5.16], 0.4329		0.94 [0.46, 1.93], 0.8748	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.06], 0.3893		0.03 [-0.05, 0.11], 0.4030		-0.01 [-0.07, 0.06], 0.8757	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6851		0.7812		0.9433	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	2/11 (18.2)	3/21 (14.3)	1/9 (11.1)	5/44 (11.4)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.08, 2.96], 0.4279		1.29 [0.15, 10.76], 0.8166		0.76 [0.20, 2.86], 0.6825	
OR [95%-CI]; p-value	0.43 [0.05, 3.53], 0.4219		1.33 [0.12, 14.87], 0.8147		0.73 [0.16, 3.39], 0.6835	
RD [95%-CI]; p-value	-0.09 [-0.35, 0.16], 0.4666		0.03 [-0.22, 0.29], 0.8065		-0.04 [-0.22, 0.15], 0.6960	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	26/118 (22.0)	19/61 (31.1)	22/123 (17.9)	12/63 (19.0)	48/241 (19.9)	31/124 (25.0)
RR [95%-CI]; p-value	0.71 [0.43, 1.17], 0.1786		0.94 [0.50, 1.77], 0.8459		0.80 [0.54, 1.18], 0.2609	
OR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1828		0.93 [0.42, 2.02], 0.8462		0.75 [0.45, 1.25], 0.2641	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.1962		-0.01 [-0.13, 0.11], 0.8474		-0.05 [-0.14, 0.04], 0.2756	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5187		0.1364		0.1410	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	5/11 (45.5)	3/21 (14.3)	4/9 (44.4)	7/44 (15.9)	9/20 (45.0)
RR [95%-CI]; p-value	0.38 [0.13, 1.15], 0.0872		0.32 [0.09, 1.15], 0.0815		0.35 [0.15, 0.81], 0.0146	
OR [95%-CI]; p-value	0.25 [0.05, 1.26], 0.0827		0.21 [0.03, 1.25], 0.0735		0.23 [0.07, 0.76], 0.0127	
RD [95%-CI]; p-value	-0.28 [-0.61, 0.05], 0.0981		-0.30 [-0.66, 0.06], 0.0982		-0.29 [-0.53, -0.05], 0.0191	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	20/118 (16.9)	18/61 (29.5)	19/123 (15.4)	10/63 (15.9)	39/241 (16.2)	28/124 (22.6)
RR [95%-CI]; p-value	0.57 [0.33, 1.00], 0.0509		0.97 [0.48, 1.97], 0.9396		0.72 [0.46, 1.11], 0.1329	
OR [95%-CI]; p-value	0.49 [0.23, 1.01], 0.0515		0.97 [0.42, 2.23], 0.9396		0.66 [0.38, 1.14], 0.1348	
RD [95%-CI]; p-value	-0.13 [-0.26, 0.01], 0.0641		-0.00 [-0.11, 0.11], 0.9398		-0.06 [-0.15, 0.02], 0.1497	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9948		0.0501		0.2189	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	3/44 (6.8)	4/20 (20.0)
RR [95%-CI]; p-value	0.48 [0.03, 6.96], 0.5892		0.29 [0.06, 1.43], 0.1272		0.34 [0.08, 1.38], 0.1321	
OR [95%-CI]; p-value	0.45 [0.03, 8.02], 0.5824		0.21 [0.03, 1.57], 0.1088		0.29 [0.06, 1.46], 0.1173	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6232		-0.24 [-0.57, 0.09], 0.1606		-0.13 [-0.32, 0.06], 0.1750	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	11/118 (9.3)	12/61 (19.7)	18/123 (14.6)	5/63 (7.9)	29/241 (12.0)	17/124 (13.7)
RR [95%-CI]; p-value	0.47 [0.22, 1.01], 0.0533		1.84 [0.72, 4.74], 0.2035		0.88 [0.50, 1.53], 0.6469	
OR [95%-CI]; p-value	0.42 [0.17, 1.02], 0.0498		1.99 [0.70, 5.63], 0.1891		0.86 [0.45, 1.64], 0.6476	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0719		0.07 [-0.02, 0.16], 0.1510		-0.02 [-0.09, 0.06], 0.6533	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.9850		0.4097		0.6641	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	2/21 (9.5)	2/9 (22.2)	3/44 (6.8)	2/20 (10.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		0.43 [0.07, 2.59], 0.3556		0.68 [0.12, 3.77], 0.6606	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		0.37 [0.04, 3.14], 0.3484		0.66 [0.10, 4.29], 0.6602	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		-0.13 [-0.43, 0.17], 0.4055		-0.03 [-0.18, 0.12], 0.6798	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	10/118 (8.5)	5/61 (8.2)	10/123 (8.1)	5/63 (7.9)	20/241 (8.3)	10/124 (8.1)
RR [95%-CI]; p-value	1.03 [0.37, 2.89], 0.9493		1.02 [0.37, 2.87], 0.9634		1.03 [0.50, 2.13], 0.9385	
OR [95%-CI]; p-value	1.04 [0.34, 3.18], 0.9493		1.03 [0.34, 3.14], 0.9634		1.03 [0.47, 2.28], 0.9385	
RD [95%-CI]; p-value	0.00 [-0.08, 0.09], 0.9491		0.00 [-0.08, 0.08], 0.9633		0.00 [-0.06, 0.06], 0.9382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4770		0.3543		0.3166	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	5/21 (23.8)	3/9 (33.3)	8/44 (18.2)	6/20 (30.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.71 [0.22, 2.37], 0.5825		0.61 [0.24, 1.52], 0.2845	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.63 [0.11, 3.46], 0.5888		0.52 [0.15, 1.77], 0.2891	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.10 [-0.45, 0.26], 0.6019		-0.12 [-0.35, 0.11], 0.3158	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	15/118 (12.7)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	27/241 (11.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.86 [0.40, 1.85], 0.7032		1.54 [0.52, 4.57], 0.4399		1.07 [0.57, 2.00], 0.8352	
OR [95%-CI]; p-value	0.84 [0.35, 2.05], 0.7039		1.59 [0.49, 5.16], 0.4329		1.08 [0.53, 2.17], 0.8349	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7094		0.03 [-0.05, 0.11], 0.4030		0.01 [-0.06, 0.07], 0.8334	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4758		0.0241		0.0222	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	2/11 (18.2)	0/21 (0.0)	3/9 (33.3)	1/44 (2.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.24 [0.02, 2.36], 0.2208		0.07 [0.00, 1.26], 0.0711		0.09 [0.01, 0.73], 0.0239	
OR [95%-CI]; p-value	0.20 [0.02, 2.55], 0.1834		0.05 [0.00, 1.09], 0.0143		0.07 [0.01, 0.65], 0.0038	
RD [95%-CI]; p-value	-0.14 [-0.38, 0.10], 0.2639		-0.31 [-0.62, 0.00], 0.0533		-0.23 [-0.42, -0.03], 0.0222	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	7/61 (11.5)	15/123 (12.2)	3/63 (4.8)	23/241 (9.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.59 [0.22, 1.55], 0.2857		2.56 [0.77, 8.52], 0.1251		1.18 [0.58, 2.41], 0.6421	
OR [95%-CI]; p-value	0.56 [0.19, 1.63], 0.2825		2.78 [0.77, 9.98], 0.1046		1.20 [0.55, 2.61], 0.6407	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.04], 0.3169		0.07 [-0.00, 0.15], 0.0623		0.01 [-0.05, 0.08], 0.6324	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9167		0.6331		0.8171	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	1/21 (4.8)	1/9 (11.1)	3/44 (6.8)	2/20 (10.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.43 [0.03, 6.12], 0.5324		0.68 [0.12, 3.77], 0.6606	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.40 [0.02, 7.20], 0.5229		0.66 [0.10, 4.29], 0.6602	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.06 [-0.29, 0.16], 0.5796		-0.03 [-0.18, 0.12], 0.6798	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	13/118 (11.0)	8/61 (13.1)	10/123 (8.1)	6/63 (9.5)	23/241 (9.5)	14/124 (11.3)
RR [95%-CI]; p-value	0.84 [0.37, 1.92], 0.6787		0.85 [0.33, 2.24], 0.7481		0.85 [0.45, 1.58], 0.5999	
OR [95%-CI]; p-value	0.82 [0.32, 2.10], 0.6793		0.84 [0.29, 2.43], 0.7483		0.83 [0.41, 1.67], 0.6005	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.08], 0.6863		-0.01 [-0.10, 0.07], 0.7538		-0.02 [-0.08, 0.05], 0.6090	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.4.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3428		0.6996		0.5170	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	0/23 (0.0)	3/11 (27.3)	2/21 (9.5)	0/9 (0.0)	2/44 (4.5)	3/20 (15.0)
RR [95%-CI]; p-value	0.08 [0.00, 1.43], 0.0855		1.81 [0.09, 36.44], 0.6987		0.30 [0.05, 1.67], 0.1710	
OR [95%-CI]; p-value	0.06 [0.00, 1.29], 0.0226		1.89 [0.08, 46.43], 0.6912		0.27 [0.04, 1.76], 0.1486	
RD [95%-CI]; p-value	-0.25 [-0.52, 0.02], 0.0675		0.04 [-0.15, 0.23], 0.6595		-0.10 [-0.27, 0.06], 0.2230	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	9/61 (14.8)	4/123 (3.3)	0/63 (0.0)	10/241 (4.1)	9/124 (7.3)
RR [95%-CI]; p-value	0.34 [0.13, 0.92], 0.0342		4.13 [0.22, 76.91], 0.3418		0.57 [0.24, 1.37], 0.2099	
OR [95%-CI]; p-value	0.31 [0.10, 0.92], 0.0269		4.24 [0.22, 81.39], 0.2986		0.55 [0.22, 1.40], 0.2054	
RD [95%-CI]; p-value	-0.10 [-0.19, 0.00], 0.0517		0.02 [-0.01, 0.06], 0.2054		-0.03 [-0.08, 0.02], 0.2426	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_4_m_pt_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.4.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2083		0.7775		0.2135	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	0/11 (0.0)	2/21 (9.5)	1/9 (11.1)	4/44 (9.1)	1/20 (5.0)
RR [95%-CI]; p-value	2.00 [0.10, 40.86], 0.6525		0.86 [0.09, 8.30], 0.8941		1.82 [0.22, 15.25], 0.5816	
OR [95%-CI]; p-value	2.10 [0.09, 50.57], 0.6424		0.84 [0.07, 10.66], 0.8943		1.90 [0.20, 18.18], 0.5719	
RD [95%-CI]; p-value	0.04 [-0.12, 0.21], 0.6051		-0.02 [-0.26, 0.22], 0.8971		0.04 [-0.09, 0.17], 0.5305	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	5/118 (4.2)	10/61 (16.4)	5/123 (4.1)	2/63 (3.2)	10/241 (4.1)	12/124 (9.7)
RR [95%-CI]; p-value	0.26 [0.09, 0.72], 0.0099		1.28 [0.26, 6.42], 0.7636		0.43 [0.19, 0.96], 0.0406	
OR [95%-CI]; p-value	0.23 [0.07, 0.69], 0.0054		1.29 [0.24, 6.86], 0.7627		0.40 [0.17, 0.96], 0.0356	
RD [95%-CI]; p-value	-0.12 [-0.22, -0.02], 0.0169		0.01 [-0.05, 0.06], 0.7536		-0.06 [-0.11, 0.00], 0.0609	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_4_m_pt_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.4.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.5492		0.8301		0.6494	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	1/11 (9.1)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	1/20 (5.0)
RR [95%-CI]; p-value	0.48 [0.03, 6.96], 0.5892		0.44 [0.01, 20.66], 0.6771		0.45 [0.03, 6.91], 0.5701	
OR [95%-CI]; p-value	0.45 [0.03, 8.02], 0.5824		0.43 [0.01, 23.33], 0.6695		0.44 [0.03, 7.44], 0.5611	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6232		-0.03 [-0.19, 0.13], 0.7114		-0.03 [-0.13, 0.08], 0.6113	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	9/118 (7.6)	4/61 (6.6)	8/123 (6.5)	6/63 (9.5)	17/241 (7.1)	10/124 (8.1)
RR [95%-CI]; p-value	1.16 [0.37, 3.62], 0.7944		0.68 [0.25, 1.88], 0.4610		0.87 [0.41, 1.85], 0.7266	
OR [95%-CI]; p-value	1.18 [0.35, 3.99], 0.7938		0.66 [0.22, 2.00], 0.4600		0.87 [0.38, 1.95], 0.7268	
RD [95%-CI]; p-value	0.01 [-0.07, 0.09], 0.7892		-0.03 [-0.11, 0.05], 0.4841		-0.01 [-0.07, 0.05], 0.7319	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_4_m_pt_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.8350		0.2630		0.5072	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	0/11 (0.0)	2/21 (9.5)	3/9 (33.3)	6/44 (13.6)	3/20 (15.0)
RR [95%-CI]; p-value	4.00 [0.23, 69.39], 0.3410		0.29 [0.06, 1.43], 0.1272		0.91 [0.25, 3.27], 0.8841	
OR [95%-CI]; p-value	4.63 [0.22, 96.08], 0.2835		0.21 [0.03, 1.57], 0.1088		0.89 [0.20, 4.01], 0.8844	
RD [95%-CI]; p-value	0.13 [-0.06, 0.33], 0.1891		-0.24 [-0.57, 0.09], 0.1606		-0.01 [-0.20, 0.17], 0.8860	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	11/118 (9.3)	2/61 (3.3)	7/123 (5.7)	4/63 (6.3)	18/241 (7.5)	6/124 (4.8)
RR [95%-CI]; p-value	2.84 [0.65, 12.42], 0.1649		0.90 [0.27, 2.95], 0.8570		1.54 [0.63, 3.79], 0.3435	
OR [95%-CI]; p-value	3.03 [0.65, 14.14], 0.1398		0.89 [0.25, 3.16], 0.8571		1.59 [0.61, 4.11], 0.3369	
RD [95%-CI]; p-value	0.06 [-0.01, 0.13], 0.0856		-0.01 [-0.08, 0.07], 0.8594		0.03 [-0.02, 0.08], 0.3052	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9863		0.9512		0.9623	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	0/20 (0.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		NA		0.93 [0.03, 26.67], 0.9671	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		NA		0.93 [0.03, 28.89], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		NA		-0.00 [-0.08, 0.08], 0.9675	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	1/118 (0.8)	0/61 (0.0)	1/123 (0.8)	1/63 (1.6)	2/241 (0.8)	1/124 (0.8)
RR [95%-CI]; p-value	1.04 [0.04, 30.64], 0.9808		0.51 [0.03, 8.05], 0.6341		1.03 [0.09, 11.24], 0.9813	
OR [95%-CI]; p-value	1.04 [0.03, 31.52], 0.9808		0.51 [0.03, 8.26], 0.6280		1.03 [0.09, 11.46], 0.9813	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9807		-0.01 [-0.04, 0.03], 0.6619		0.00 [-0.02, 0.02], 0.9812	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9288		0.2339		0.3572	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	0/11 (0.0)	2/21 (9.5)	3/9 (33.3)	5/44 (11.4)	3/20 (15.0)
RR [95%-CI]; p-value	3.00 [0.16, 55.02], 0.4592		0.29 [0.06, 1.43], 0.1272		0.76 [0.20, 2.86], 0.6825	
OR [95%-CI]; p-value	3.30 [0.15, 72.02], 0.4252		0.21 [0.03, 1.57], 0.1088		0.73 [0.16, 3.39], 0.6835	
RD [95%-CI]; p-value	0.09 [-0.09, 0.27], 0.3469		-0.24 [-0.57, 0.09], 0.1606		-0.04 [-0.22, 0.15], 0.6960	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	10/118 (8.5)	2/61 (3.3)	6/123 (4.9)	3/63 (4.8)	16/241 (6.6)	5/124 (4.0)
RR [95%-CI]; p-value	2.58 [0.58, 11.43], 0.2105		1.02 [0.26, 3.96], 0.9721		1.65 [0.62, 4.39], 0.3189	
OR [95%-CI]; p-value	2.73 [0.58, 12.88], 0.1877		1.03 [0.25, 4.24], 0.9721		1.69 [0.61, 4.73], 0.3111	
RD [95%-CI]; p-value	0.05 [-0.02, 0.12], 0.1299		0.00 [-0.06, 0.07], 0.9720		0.03 [-0.02, 0.07], 0.2746	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.5720		0.4326		0.4243	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	0/20 (0.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		NA		0.93 [0.03, 26.67], 0.9671	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		NA		0.93 [0.03, 28.89], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		NA		-0.00 [-0.08, 0.08], 0.9675	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	1/61 (1.6)	3/123 (2.4)	0/63 (0.0)	9/241 (3.7)	1/124 (0.8)
RR [95%-CI]; p-value	3.10 [0.38, 25.19], 0.2894		3.10 [0.16, 60.90], 0.4569		4.63 [0.59, 36.14], 0.1437	
OR [95%-CI]; p-value	3.21 [0.38, 27.32], 0.2597		3.15 [0.16, 63.87], 0.4309		4.77 [0.60, 38.10], 0.1046	
RD [95%-CI]; p-value	0.03 [-0.02, 0.09], 0.1843		0.02 [-0.02, 0.05], 0.3532		0.03 [0.00, 0.06], 0.0452	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9267		0.2929		0.3004	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	3/11 (27.3)	0/21 (0.0)	1/9 (11.1)	4/44 (9.1)	4/20 (20.0)
RR [95%-CI]; p-value	0.64 [0.17, 2.37], 0.5019		0.21 [0.01, 5.70], 0.3536		0.45 [0.13, 1.64], 0.2277	
OR [95%-CI]; p-value	0.56 [0.10, 3.10], 0.5050		0.19 [0.01, 6.25], 0.3062		0.40 [0.09, 1.80], 0.2213	
RD [95%-CI]; p-value	-0.10 [-0.40, 0.21], 0.5260		-0.09 [-0.30, 0.13], 0.4231		-0.11 [-0.30, 0.09], 0.2724	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	6/61 (9.8)	13/123 (10.6)	5/63 (7.9)	21/241 (8.7)	11/124 (8.9)
RR [95%-CI]; p-value	0.69 [0.25, 1.90], 0.4713		1.33 [0.50, 3.57], 0.5689		0.98 [0.49, 1.97], 0.9599	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4704		1.37 [0.47, 4.03], 0.5655		0.98 [0.46, 2.11], 0.9599	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.4932		0.03 [-0.06, 0.11], 0.5488		-0.00 [-0.06, 0.06], 0.9600	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9863		0.4959		0.6167	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	0/20 (0.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		NA		0.93 [0.03, 26.67], 0.9671	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		NA		0.93 [0.03, 28.89], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		NA		-0.00 [-0.08, 0.08], 0.9675	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	1/118 (0.8)	0/61 (0.0)	4/123 (3.3)	1/63 (1.6)	5/241 (2.1)	1/124 (0.8)
RR [95%-CI]; p-value	1.04 [0.04, 30.64], 0.9808		2.05 [0.23, 17.95], 0.5171		2.57 [0.30, 21.78], 0.3859	
OR [95%-CI]; p-value	1.04 [0.03, 31.52], 0.9808		2.08 [0.23, 19.05], 0.5065		2.61 [0.30, 22.55], 0.3668	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9807		0.02 [-0.03, 0.06], 0.4583		0.01 [-0.01, 0.04], 0.2985	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7975		0.3685		0.2928	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	0/21 (0.0)	1/9 (11.1)	3/44 (6.8)	4/20 (20.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.21 [0.01, 5.70], 0.3536		0.34 [0.08, 1.38], 0.1321	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.19 [0.01, 6.25], 0.3062		0.29 [0.06, 1.46], 0.1173	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.09 [-0.30, 0.13], 0.4231		-0.13 [-0.32, 0.06], 0.1750	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	7/118 (5.9)	6/61 (9.8)	10/123 (8.1)	5/63 (7.9)	17/241 (7.1)	11/124 (8.9)
RR [95%-CI]; p-value	0.60 [0.21, 1.72], 0.3433		1.02 [0.37, 2.87], 0.9634		0.80 [0.38, 1.64], 0.5365	
OR [95%-CI]; p-value	0.58 [0.19, 1.80], 0.3401		1.03 [0.34, 3.14], 0.9634		0.78 [0.35, 1.72], 0.5367	
RD [95%-CI]; p-value	-0.04 [-0.13, 0.05], 0.3738		0.00 [-0.08, 0.08], 0.9633		-0.02 [-0.08, 0.04], 0.5500	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
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Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8664		0.4331		0.8906	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	3/44 (6.8)	0/20 (0.0)
RR [95%-CI]; p-value	3.00 [0.16, 55.02], 0.4592		NA		2.80 [0.15, 53.29], 0.4943	
OR [95%-CI]; p-value	3.30 [0.15, 72.02], 0.4252		NA		2.93 [0.14, 61.26], 0.4697	
RD [95%-CI]; p-value	0.09 [-0.09, 0.27], 0.3469		NA		0.04 [-0.06, 0.14], 0.3909	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	2/118 (1.7)	0/61 (0.0)	5/123 (4.1)	1/63 (1.6)	7/241 (2.9)	1/124 (0.8)
RR [95%-CI]; p-value	2.08 [0.10, 45.52], 0.6405		2.56 [0.31, 21.45], 0.3858		3.60 [0.45, 28.95], 0.2282	
OR [95%-CI]; p-value	2.10 [0.09, 47.37], 0.6323		2.63 [0.30, 22.98], 0.3654		3.68 [0.45, 30.25], 0.1948	
RD [95%-CI]; p-value	0.01 [-0.02, 0.04], 0.5931		0.02 [-0.02, 0.07], 0.2972		0.02 [-0.01, 0.05], 0.1194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.6.s8
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.2955		0.9762		0.5427	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	4/11 (36.4)	7/21 (33.3)	2/9 (22.2)	10/44 (22.7)	6/20 (30.0)
RR [95%-CI]; p-value	0.36 [0.10, 1.33], 0.1260		1.50 [0.38, 5.87], 0.5601		0.76 [0.32, 1.80], 0.5284	
OR [95%-CI]; p-value	0.26 [0.05, 1.48], 0.1157		1.75 [0.29, 10.74], 0.5428		0.69 [0.21, 2.25], 0.5334	
RD [95%-CI]; p-value	-0.23 [-0.55, 0.08], 0.1479		0.11 [-0.23, 0.45], 0.5197		-0.07 [-0.31, 0.16], 0.5457	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	21/118 (17.8)	14/61 (23.0)	21/123 (17.1)	7/63 (11.1)	42/241 (17.4)	21/124 (16.9)
RR [95%-CI]; p-value	0.78 [0.42, 1.42], 0.4072		1.54 [0.69, 3.42], 0.2924		1.03 [0.64, 1.66], 0.9063	
OR [95%-CI]; p-value	0.73 [0.34, 1.56], 0.4099		1.65 [0.66, 4.11], 0.2819		1.04 [0.58, 1.84], 0.9062	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4230		0.06 [-0.04, 0.16], 0.2529		0.00 [-0.08, 0.09], 0.9059	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_6_m_pt_adr_vitd.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.8075		0.9529		0.7492	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	53/68 (77.9)	34/40 (85.0)	46/70 (65.7)	23/36 (63.9)	99/138 (71.7)	57/76 (75.0)
RR [95%-CI]; p-value	0.92 [0.76, 1.10], 0.3491		1.03 [0.76, 1.39], 0.8531		0.96 [0.81, 1.13], 0.6014	
OR [95%-CI]; p-value	0.62 [0.22, 1.76], 0.3707		1.08 [0.47, 2.51], 0.8519		0.85 [0.45, 1.60], 0.6075	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3505		0.02 [-0.17, 0.21], 0.8524		-0.03 [-0.16, 0.09], 0.6032	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	48/73 (65.8)	22/32 (68.8)	45/74 (60.8)	21/36 (58.3)	93/147 (63.3)	43/68 (63.2)
RR [95%-CI]; p-value	0.96 [0.72, 1.27], 0.7603		1.04 [0.75, 1.45], 0.8056		1.00 [0.80, 1.25], 0.9966	
OR [95%-CI]; p-value	0.87 [0.36, 2.13], 0.7643		1.11 [0.49, 2.49], 0.8035		1.00 [0.55, 1.82], 0.9966	
RD [95%-CI]; p-value	-0.03 [-0.22, 0.16], 0.7621		0.02 [-0.17, 0.22], 0.8041		0.00 [-0.14, 0.14], 0.9966	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.5179		0.9728		0.8309	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	10/68 (14.7)	6/40 (15.0)	9/70 (12.9)	1/36 (2.8)	19/138 (13.8)	7/76 (9.2)
RR [95%-CI]; p-value	0.98 [0.39, 2.49], 0.9668		4.63 [0.61, 35.12], 0.1384		1.49 [0.66, 3.39], 0.3367	
OR [95%-CI]; p-value	0.98 [0.33, 2.93], 0.9669		5.16 [0.63, 42.48], 0.0927		1.57 [0.63, 3.93], 0.3288	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.14], 0.9669		0.10 [0.01, 0.20], 0.0376		0.05 [-0.04, 0.13], 0.3033	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	5/32 (15.6)	10/74 (13.5)	1/36 (2.8)	17/147 (11.6)	6/68 (8.8)
RR [95%-CI]; p-value	0.61 [0.21, 1.79], 0.3710		4.86 [0.65, 36.55], 0.1242		1.31 [0.54, 3.18], 0.5492	
OR [95%-CI]; p-value	0.57 [0.17, 1.96], 0.3709		5.47 [0.67, 44.50], 0.0782		1.35 [0.51, 3.60], 0.5454	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.08], 0.4074		0.11 [0.01, 0.20], 0.0261		0.03 [-0.06, 0.11], 0.5271	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.1281		0.7175		0.3731	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	5/40 (12.5)	5/70 (7.1)	3/36 (8.3)	12/138 (8.7)	8/76 (10.5)
RR [95%-CI]; p-value	0.82 [0.28, 2.42], 0.7244		0.86 [0.22, 3.39], 0.8259		0.83 [0.35, 1.93], 0.6594	
OR [95%-CI]; p-value	0.80 [0.24, 2.72], 0.7246		0.85 [0.19, 3.76], 0.8261		0.81 [0.32, 2.08], 0.6597	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.10], 0.7302		-0.01 [-0.12, 0.10], 0.8299		-0.02 [-0.10, 0.07], 0.6674	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	11/73 (15.1)	1/32 (3.1)	5/74 (6.8)	4/36 (11.1)	16/147 (10.9)	5/68 (7.4)
RR [95%-CI]; p-value	4.82 [0.65, 35.79], 0.1240		0.61 [0.17, 2.13], 0.4365		1.48 [0.57, 3.87], 0.4243	
OR [95%-CI]; p-value	5.50 [0.68, 44.56], 0.0766		0.58 [0.15, 2.30], 0.4343		1.54 [0.54, 4.39], 0.4173	
RD [95%-CI]; p-value	0.12 [0.02, 0.22], 0.0215		-0.04 [-0.16, 0.07], 0.4677		0.04 [-0.04, 0.12], 0.3863	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.9668		0.6509		0.7528	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	13/68 (19.1)	6/40 (15.0)	10/70 (14.3)	6/36 (16.7)	23/138 (16.7)	12/76 (15.8)
RR [95%-CI]; p-value	1.27 [0.53, 3.09], 0.5911		0.86 [0.34, 2.17], 0.7450		1.06 [0.56, 2.00], 0.8684	
OR [95%-CI]; p-value	1.34 [0.47, 3.86], 0.5873		0.83 [0.28, 2.51], 0.7457		1.07 [0.50, 2.29], 0.8681	
RD [95%-CI]; p-value	0.04 [-0.10, 0.19], 0.5774		-0.02 [-0.17, 0.12], 0.7505		0.01 [-0.09, 0.11], 0.8673	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	17/73 (23.3)	6/32 (18.8)	12/74 (16.2)	5/36 (13.9)	29/147 (19.7)	11/68 (16.2)
RR [95%-CI]; p-value	1.24 [0.54, 2.86], 0.6100		1.17 [0.45, 3.06], 0.7528		1.22 [0.65, 2.29], 0.5380	
OR [95%-CI]; p-value	1.32 [0.46, 3.72], 0.6048		1.20 [0.39, 3.71], 0.7514		1.27 [0.59, 2.73], 0.5338	
RD [95%-CI]; p-value	0.05 [-0.12, 0.21], 0.5930		0.02 [-0.12, 0.16], 0.7459		0.04 [-0.07, 0.14], 0.5216	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.0281		0.9429		0.0354	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	5/40 (12.5)	7/70 (10.0)	2/36 (5.6)	10/138 (7.2)	7/76 (9.2)
RR [95%-CI]; p-value	0.35 [0.09, 1.40], 0.1383		1.80 [0.39, 8.22], 0.4483		0.79 [0.31, 1.98], 0.6111	
OR [95%-CI]; p-value	0.32 [0.07, 1.43], 0.1212		1.89 [0.37, 9.60], 0.4369		0.77 [0.28, 2.11], 0.6111	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1626		0.04 [-0.06, 0.15], 0.3961		-0.02 [-0.10, 0.06], 0.6220	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	13/73 (17.8)	0/32 (0.0)	8/74 (10.8)	2/36 (5.6)	21/147 (14.3)	2/68 (2.9)
RR [95%-CI]; p-value	11.58 [0.71, 189.25], 0.0858		1.95 [0.44, 8.70], 0.3835		4.86 [1.17, 20.13], 0.0293	
OR [95%-CI]; p-value	13.87 [0.80, 241.41], 0.0209		2.06 [0.41, 10.24], 0.3683		5.50 [1.25, 24.18], 0.0123	
RD [95%-CI]; p-value	0.16 [0.07, 0.26], 0.0011		0.05 [-0.05, 0.16], 0.3172		0.11 [0.04, 0.18], 0.0013	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.2089		0.5129		0.1208	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	2/68 (2.9)	2/40 (5.0)	3/70 (4.3)	2/36 (5.6)	5/138 (3.6)	4/76 (5.3)
RR [95%-CI]; p-value	0.59 [0.09, 4.01], 0.5882		0.77 [0.13, 4.41], 0.7705		0.69 [0.19, 2.49], 0.5689	
OR [95%-CI]; p-value	0.58 [0.08, 4.26], 0.5843		0.76 [0.12, 4.77], 0.7702		0.68 [0.18, 2.60], 0.5673	
RD [95%-CI]; p-value	-0.02 [-0.10, 0.06], 0.6076		-0.01 [-0.10, 0.08], 0.7788		-0.02 [-0.08, 0.04], 0.5865	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	0/32 (0.0)	4/74 (5.4)	1/36 (2.8)	10/147 (6.8)	1/68 (1.5)
RR [95%-CI]; p-value	5.34 [0.31, 92.84], 0.2500		1.95 [0.23, 16.79], 0.5448		4.63 [0.60, 35.41], 0.1402	
OR [95%-CI]; p-value	5.73 [0.31, 105.80], 0.1876		2.00 [0.22, 18.57], 0.5347		4.89 [0.61, 39.00], 0.0989	
RD [95%-CI]; p-value	0.07 [-0.01, 0.14], 0.0845		0.03 [-0.05, 0.10], 0.4888		0.05 [0.00, 0.10], 0.0357	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.3340		0.5223		0.1392	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	0/68 (0.0)	1/40 (2.5)	1/70 (1.4)	1/36 (2.8)	1/138 (0.7)	2/76 (2.6)
RR [95%-CI]; p-value	0.29 [0.01, 8.51], 0.4743		0.51 [0.03, 7.98], 0.6346		0.28 [0.03, 2.99], 0.2890	
OR [95%-CI]; p-value	0.29 [0.01, 8.74], 0.4462		0.51 [0.03, 8.35], 0.6287		0.27 [0.02, 3.03], 0.2562	
RD [95%-CI]; p-value	-0.02 [-0.07, 0.03], 0.5080		-0.01 [-0.07, 0.05], 0.6618		-0.02 [-0.06, 0.02], 0.3338	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	0/32 (0.0)	2/74 (2.7)	0/36 (0.0)	5/147 (3.4)	0/68 (0.0)
RR [95%-CI]; p-value	2.67 [0.14, 51.82], 0.5161		1.97 [0.09, 42.65], 0.6648		4.66 [0.26, 84.09], 0.2971	
OR [95%-CI]; p-value	2.74 [0.13, 56.37], 0.4960		2.00 [0.09, 45.51], 0.6577		4.79 [0.26, 88.92], 0.2469	
RD [95%-CI]; p-value	0.03 [-0.04, 0.09], 0.4176		0.01 [-0.04, 0.07], 0.6207		0.03 [-0.01, 0.06], 0.1410	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.9990		0.1832		0.4295	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	45/68 (66.2)	31/40 (77.5)	36/70 (51.4)	15/36 (41.7)	81/138 (58.7)	46/76 (60.5)
RR [95%-CI]; p-value	0.85 [0.67, 1.08], 0.1938		1.23 [0.79, 1.93], 0.3577		0.97 [0.77, 1.22], 0.7929	
OR [95%-CI]; p-value	0.57 [0.23, 1.39], 0.2133		1.48 [0.66, 3.34], 0.3408		0.93 [0.52, 1.64], 0.7942	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.1955		0.10 [-0.10, 0.30], 0.3366		-0.02 [-0.16, 0.12], 0.7937	
2.Baseline 25D ≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	37/73 (50.7)	19/32 (59.4)	34/74 (45.9)	20/36 (55.6)	71/147 (48.3)	39/68 (57.4)
RR [95%-CI]; p-value	0.85 [0.59, 1.23], 0.3957		0.83 [0.56, 1.21], 0.3307		0.84 [0.65, 1.10], 0.2030	
OR [95%-CI]; p-value	0.70 [0.30, 1.63], 0.4113		0.68 [0.31, 1.51], 0.3442		0.69 [0.39, 1.24], 0.2168	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.12], 0.4065		-0.10 [-0.29, 0.10], 0.3417		-0.09 [-0.23, 0.05], 0.2135	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.8138		0.6592		0.8382	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	25/68 (36.8)	16/40 (40.0)	24/70 (34.3)	10/36 (27.8)	49/138 (35.5)	26/76 (34.2)
RR [95%-CI]; p-value	0.92 [0.56, 1.50], 0.7364		1.23 [0.66, 2.29], 0.5048		1.04 [0.71, 1.52], 0.8496	
OR [95%-CI]; p-value	0.87 [0.39, 1.94], 0.7380		1.36 [0.56, 3.27], 0.4966		1.06 [0.59, 1.91], 0.8491	
RD [95%-CI]; p-value	-0.03 [-0.22, 0.16], 0.7389		0.07 [-0.12, 0.25], 0.4876		0.01 [-0.12, 0.15], 0.8487	
2.Baseline 25D ≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	25/73 (34.2)	13/32 (40.6)	25/74 (33.8)	8/36 (22.2)	50/147 (34.0)	21/68 (30.9)
RR [95%-CI]; p-value	0.84 [0.50, 1.43], 0.5244		1.52 [0.76, 3.03], 0.2337		1.10 [0.72, 1.68], 0.6529	
OR [95%-CI]; p-value	0.76 [0.32, 1.79], 0.5313		1.79 [0.71, 4.49], 0.2144		1.15 [0.62, 2.14], 0.6498	
RD [95%-CI]; p-value	-0.06 [-0.27, 0.14], 0.5360		0.12 [-0.06, 0.29], 0.1912		0.03 [-0.10, 0.17], 0.6467	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.1281		0.7175		0.3731	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	5/40 (12.5)	5/70 (7.1)	3/36 (8.3)	12/138 (8.7)	8/76 (10.5)
RR [95%-CI]; p-value	0.82 [0.28, 2.42], 0.7244		0.86 [0.22, 3.39], 0.8259		0.83 [0.35, 1.93], 0.6594	
OR [95%-CI]; p-value	0.80 [0.24, 2.72], 0.7246		0.85 [0.19, 3.76], 0.8261		0.81 [0.32, 2.08], 0.6597	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.10], 0.7302		-0.01 [-0.12, 0.10], 0.8299		-0.02 [-0.10, 0.07], 0.6674	
2.Baseline 25D ≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	11/73 (15.1)	1/32 (3.1)	5/74 (6.8)	4/36 (11.1)	16/147 (10.9)	5/68 (7.4)
RR [95%-CI]; p-value	4.82 [0.65, 35.79], 0.1240		0.61 [0.17, 2.13], 0.4365		1.48 [0.57, 3.87], 0.4243	
OR [95%-CI]; p-value	5.50 [0.68, 44.56], 0.0766		0.58 [0.15, 2.30], 0.4343		1.54 [0.54, 4.39], 0.4173	
RD [95%-CI]; p-value	0.12 [0.02, 0.22], 0.0215		-0.04 [-0.16, 0.07], 0.4677		0.04 [-0.04, 0.12], 0.3863	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1195		0.4984		0.1099	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	6/70 (8.6)	3/36 (8.3)	10/138 (7.2)	10/76 (13.2)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.03 [0.27, 3.87], 0.9668		0.55 [0.24, 1.26], 0.1593	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.03 [0.24, 4.39], 0.9668		0.52 [0.20, 1.30], 0.1551	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.00 [-0.11, 0.11], 0.9666		-0.06 [-0.15, 0.03], 0.1852	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	2/32 (6.3)	5/74 (6.8)	1/36 (2.8)	12/147 (8.2)	3/68 (4.4)
RR [95%-CI]; p-value	1.53 [0.34, 6.98], 0.5799		2.43 [0.29, 20.06], 0.4089		1.85 [0.54, 6.34], 0.3276	
OR [95%-CI]; p-value	1.59 [0.31, 8.12], 0.5737		2.54 [0.29, 22.55], 0.3885		1.93 [0.53, 7.06], 0.3153	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5434		0.04 [-0.04, 0.12], 0.3201		0.04 [-0.03, 0.10], 0.2645	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6434		0.4204		0.4477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	15/68 (22.1)	11/40 (27.5)	15/70 (21.4)	3/36 (8.3)	30/138 (21.7)	14/76 (18.4)
RR [95%-CI]; p-value	0.80 [0.41, 1.57], 0.5208		2.57 [0.80, 8.31], 0.1144		1.18 [0.67, 2.09], 0.5685	
OR [95%-CI]; p-value	0.75 [0.30, 1.84], 0.5230		3.00 [0.81, 11.15], 0.0890		1.23 [0.61, 2.49], 0.5655	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5302		0.13 [-0.00, 0.26], 0.0516		0.03 [-0.08, 0.14], 0.5581	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	13/73 (17.8)	9/32 (28.1)	11/74 (14.9)	4/36 (11.1)	24/147 (16.3)	13/68 (19.1)
RR [95%-CI]; p-value	0.63 [0.30, 1.33], 0.2270		1.34 [0.46, 3.91], 0.5949		0.85 [0.46, 1.57], 0.6125	
OR [95%-CI]; p-value	0.55 [0.21, 1.47], 0.2318		1.40 [0.41, 4.74], 0.5904		0.83 [0.39, 1.74], 0.6141	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2581		0.04 [-0.09, 0.17], 0.5738		-0.03 [-0.14, 0.08], 0.6219	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1769		0.7513		0.2112	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	9/68 (13.2)	5/40 (12.5)	10/70 (14.3)	6/36 (16.7)	19/138 (13.8)	11/76 (14.5)
RR [95%-CI]; p-value	1.06 [0.38, 2.94], 0.9126		0.86 [0.34, 2.17], 0.7450		0.95 [0.48, 1.89], 0.8867	
OR [95%-CI]; p-value	1.07 [0.33, 3.44], 0.9125		0.83 [0.28, 2.51], 0.7457		0.94 [0.42, 2.10], 0.8869	
RD [95%-CI]; p-value	0.01 [-0.12, 0.14], 0.9120		-0.02 [-0.17, 0.12], 0.7505		-0.01 [-0.10, 0.09], 0.8875	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	10/32 (31.3)	7/74 (9.5)	5/36 (13.9)	17/147 (11.6)	15/68 (22.1)
RR [95%-CI]; p-value	0.44 [0.20, 0.95], 0.0362		0.68 [0.23, 2.00], 0.4843		0.52 [0.28, 0.99], 0.0452	
OR [95%-CI]; p-value	0.35 [0.13, 0.95], 0.0350		0.65 [0.19, 2.20], 0.4844		0.46 [0.22, 0.99], 0.0444	
RD [95%-CI]; p-value	-0.18 [-0.35, 0.00], 0.0545		-0.04 [-0.18, 0.09], 0.5081		-0.10 [-0.22, 0.01], 0.0646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1286		0.1763		0.0462	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	23/68 (33.8)	10/40 (25.0)	20/70 (28.6)	7/36 (19.4)	43/138 (31.2)	17/76 (22.4)
RR [95%-CI]; p-value	1.35 [0.72, 2.54], 0.3481		1.47 [0.69, 3.15], 0.3217		1.39 [0.86, 2.27], 0.1820	
OR [95%-CI]; p-value	1.53 [0.64, 3.68], 0.3364		1.66 [0.63, 4.39], 0.3071		1.57 [0.82, 3.01], 0.1707	
RD [95%-CI]; p-value	0.09 [-0.09, 0.26], 0.3233		0.09 [-0.08, 0.26], 0.2843		0.09 [-0.03, 0.21], 0.1560	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	15/73 (20.5)	10/32 (31.3)	13/74 (17.6)	9/36 (25.0)	28/147 (19.0)	19/68 (27.9)
RR [95%-CI]; p-value	0.66 [0.33, 1.30], 0.2295		0.70 [0.33, 1.49], 0.3570		0.68 [0.41, 1.13], 0.1383	
OR [95%-CI]; p-value	0.57 [0.22, 1.45], 0.2359		0.64 [0.24, 1.67], 0.3605		0.61 [0.31, 1.19], 0.1423	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.08], 0.2580		-0.07 [-0.24, 0.09], 0.3799		-0.09 [-0.21, 0.04], 0.1602	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.2221		0.2372		0.0870	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	4/40 (10.0)	3/70 (4.3)	2/36 (5.6)	10/138 (7.2)	6/76 (7.9)
RR [95%-CI]; p-value	1.03 [0.32, 3.30], 0.9611		0.77 [0.13, 4.41], 0.7705		0.92 [0.35, 2.43], 0.8629	
OR [95%-CI]; p-value	1.03 [0.28, 3.77], 0.9611		0.76 [0.12, 4.77], 0.7702		0.91 [0.32, 2.61], 0.8630	
RD [95%-CI]; p-value	0.00 [-0.11, 0.12], 0.9609		-0.01 [-0.10, 0.08], 0.7788		-0.01 [-0.08, 0.07], 0.8645	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	1/32 (3.1)	8/74 (10.8)	1/36 (2.8)	18/147 (12.2)	2/68 (2.9)
RR [95%-CI]; p-value	4.38 [0.59, 32.82], 0.1502		3.89 [0.51, 29.94], 0.1918		4.16 [0.99, 17.44], 0.0510	
OR [95%-CI]; p-value	4.92 [0.60, 40.19], 0.1034		4.24 [0.51, 35.30], 0.1492		4.60 [1.04, 20.45], 0.0290	
RD [95%-CI]; p-value	0.11 [0.01, 0.21], 0.0368		0.08 [-0.01, 0.17], 0.0763		0.09 [0.03, 0.16], 0.0061	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5193		0.6986		0.5039	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	7/70 (10.0)	3/36 (8.3)	18/138 (13.0)	9/76 (11.8)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		1.20 [0.33, 4.37], 0.7820		1.10 [0.52, 2.33], 0.8005	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		1.22 [0.30, 5.04], 0.7810		1.12 [0.48, 2.62], 0.8000	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.02 [-0.10, 0.13], 0.7753		0.01 [-0.08, 0.10], 0.7976	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	4/32 (12.5)	7/74 (9.5)	4/36 (11.1)	13/147 (8.8)	8/68 (11.8)
RR [95%-CI]; p-value	0.66 [0.20, 2.17], 0.4917		0.85 [0.27, 2.72], 0.7861		0.75 [0.33, 1.73], 0.5016	
OR [95%-CI]; p-value	0.63 [0.16, 2.39], 0.4915		0.84 [0.23, 3.06], 0.7864		0.73 [0.29, 1.85], 0.5023	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5211		-0.02 [-0.14, 0.11], 0.7914		-0.03 [-0.12, 0.06], 0.5213	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.3592		0.7852		0.3259	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	18/68 (26.5)	17/40 (42.5)	14/70 (20.0)	8/36 (22.2)	32/138 (23.2)	25/76 (32.9)
RR [95%-CI]; p-value	0.62 [0.36, 1.06], 0.0832		0.90 [0.42, 1.94], 0.7886		0.70 [0.45, 1.10], 0.1210	
OR [95%-CI]; p-value	0.49 [0.21, 1.11], 0.0857		0.88 [0.33, 2.33], 0.7893		0.62 [0.33, 1.15], 0.1243	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.03], 0.0906		-0.02 [-0.19, 0.14], 0.7918		-0.10 [-0.22, 0.03], 0.1340	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	4/32 (12.5)	11/74 (14.9)	5/36 (13.9)	21/147 (14.3)	9/68 (13.2)
RR [95%-CI]; p-value	1.10 [0.37, 3.24], 0.8683		1.07 [0.40, 2.85], 0.8919		1.08 [0.52, 2.23], 0.8367	
OR [95%-CI]; p-value	1.11 [0.32, 3.85], 0.8679		1.08 [0.35, 3.39], 0.8916		1.09 [0.47, 2.53], 0.8362	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8659		0.01 [-0.13, 0.15], 0.8906		0.01 [-0.09, 0.11], 0.8343	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0583		0.3407		0.0358	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	15/40 (37.5)	9/70 (12.9)	8/36 (22.2)	17/138 (12.3)	23/76 (30.3)
RR [95%-CI]; p-value	0.31 [0.15, 0.67], 0.0029		0.58 [0.24, 1.37], 0.2142		0.41 [0.23, 0.71], 0.0017	
OR [95%-CI]; p-value	0.22 [0.08, 0.59], 0.0016		0.52 [0.18, 1.48], 0.2134		0.32 [0.16, 0.66], 0.0013	
RD [95%-CI]; p-value	-0.26 [-0.43, -0.09], 0.0027		-0.09 [-0.25, 0.06], 0.2418		-0.18 [-0.30, -0.06], 0.0026	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	16/73 (21.9)	8/32 (25.0)	13/74 (17.6)	6/36 (16.7)	29/147 (19.7)	14/68 (20.6)
RR [95%-CI]; p-value	0.88 [0.42, 1.84], 0.7275		1.05 [0.44, 2.55], 0.9068		0.96 [0.54, 1.69], 0.8832	
OR [95%-CI]; p-value	0.84 [0.32, 2.23], 0.7292		1.07 [0.37, 3.08], 0.9066		0.95 [0.46, 1.94], 0.8834	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7336		0.01 [-0.14, 0.16], 0.9060		-0.01 [-0.12, 0.11], 0.8841	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.4751		0.9511		0.8297	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	12/70 (17.1)	5/36 (13.9)	16/138 (11.6)	12/76 (15.8)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.23 [0.47, 3.23], 0.6683		0.73 [0.37, 1.47], 0.3832	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.28 [0.41, 3.97], 0.6655		0.70 [0.31, 1.57], 0.3838	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.03 [-0.11, 0.18], 0.6565		-0.04 [-0.14, 0.06], 0.4007	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	8/73 (11.0)	6/32 (18.8)	8/74 (10.8)	3/36 (8.3)	16/147 (10.9)	9/68 (13.2)
RR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2796		1.30 [0.37, 4.60], 0.6869		0.82 [0.38, 1.77], 0.6161	
OR [95%-CI]; p-value	0.53 [0.17, 1.69], 0.2797		1.33 [0.33, 5.36], 0.6844		0.80 [0.33, 1.92], 0.6170	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.08], 0.3184		0.02 [-0.09, 0.14], 0.6720		-0.02 [-0.12, 0.07], 0.6276	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.2828		0.2380		0.1477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	9/70 (12.9)	2/36 (5.6)	20/138 (14.5)	8/76 (10.5)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		2.31 [0.53, 10.15], 0.2660		1.38 [0.64, 2.98], 0.4161	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		2.51 [0.51, 12.28], 0.2431		1.44 [0.60, 3.45], 0.4103	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.07 [-0.04, 0.18], 0.1867		0.04 [-0.05, 0.13], 0.3909	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	6/32 (18.8)	8/74 (10.8)	5/36 (13.9)	15/147 (10.2)	11/68 (16.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.40], 0.1923		0.78 [0.27, 2.21], 0.6381		0.63 [0.31, 1.30], 0.2116	
OR [95%-CI]; p-value	0.46 [0.14, 1.50], 0.1895		0.75 [0.23, 2.49], 0.6389		0.59 [0.25, 1.36], 0.2117	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.06], 0.2349		-0.03 [-0.16, 0.10], 0.6508		-0.06 [-0.16, 0.04], 0.2431	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4122		0.5245		0.3607	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	5/68 (7.4)	4/40 (10.0)	7/70 (10.0)	2/36 (5.6)	12/138 (8.7)	6/76 (7.9)
RR [95%-CI]; p-value	0.74 [0.21, 2.58], 0.6312		1.80 [0.39, 8.22], 0.4483		1.10 [0.43, 2.82], 0.8402	
OR [95%-CI]; p-value	0.71 [0.18, 2.83], 0.6308		1.89 [0.37, 9.60], 0.4369		1.11 [0.40, 3.09], 0.8399	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.09], 0.6425		0.04 [-0.06, 0.15], 0.3961		0.01 [-0.07, 0.08], 0.8379	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	4/73 (5.5)	5/32 (15.6)	8/74 (10.8)	4/36 (11.1)	12/147 (8.2)	9/68 (13.2)
RR [95%-CI]; p-value	0.35 [0.10, 1.22], 0.0997		0.97 [0.31, 3.02], 0.9622		0.62 [0.27, 1.39], 0.2452	
OR [95%-CI]; p-value	0.31 [0.08, 1.25], 0.0874		0.97 [0.27, 3.46], 0.9622		0.58 [0.23, 1.46], 0.2440	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.03], 0.1443		-0.00 [-0.13, 0.12], 0.9623		-0.05 [-0.14, 0.04], 0.2794	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7480		0.7289		0.9661	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	6/40 (15.0)	7/70 (10.0)	4/36 (11.1)	15/138 (10.9)	10/76 (13.2)
RR [95%-CI]; p-value	0.78 [0.29, 2.10], 0.6284		0.90 [0.28, 2.87], 0.8588		0.83 [0.39, 1.75], 0.6174	
OR [95%-CI]; p-value	0.76 [0.24, 2.36], 0.6288		0.89 [0.24, 3.26], 0.8590		0.80 [0.34, 1.89], 0.6180	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.10], 0.6375		-0.01 [-0.14, 0.11], 0.8610		-0.02 [-0.11, 0.07], 0.6261	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	3/32 (9.4)	4/74 (5.4)	3/36 (8.3)	11/147 (7.5)	6/68 (8.8)
RR [95%-CI]; p-value	1.02 [0.28, 3.70], 0.9726		0.65 [0.15, 2.75], 0.5566		0.85 [0.33, 2.20], 0.7345	
OR [95%-CI]; p-value	1.03 [0.25, 4.25], 0.9726		0.63 [0.13, 2.97], 0.5550		0.84 [0.30, 2.36], 0.7348	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9725		-0.03 [-0.13, 0.07], 0.5809		-0.01 [-0.09, 0.07], 0.7417	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.3.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9649		0.7289		0.8279	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	7/40 (17.5)	4/70 (5.7)	0/36 (0.0)	7/138 (5.1)	7/76 (9.2)
RR [95%-CI]; p-value	0.25 [0.07, 0.92], 0.0370		4.17 [0.23, 76.77], 0.3365		0.55 [0.20, 1.51], 0.2468	
OR [95%-CI]; p-value	0.22 [0.05, 0.90], 0.0234		4.36 [0.22, 84.87], 0.2902		0.53 [0.18, 1.56], 0.2414	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.00], 0.0442		0.04 [-0.02, 0.11], 0.1982		-0.04 [-0.12, 0.03], 0.2770	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	5/32 (15.6)	2/74 (2.7)	0/36 (0.0)	5/147 (3.4)	5/68 (7.4)
RR [95%-CI]; p-value	0.26 [0.07, 1.03], 0.0560		1.97 [0.09, 42.65], 0.6648		0.46 [0.14, 1.54], 0.2102	
OR [95%-CI]; p-value	0.23 [0.05, 1.04], 0.0406		2.00 [0.09, 45.51], 0.6577		0.44 [0.12, 1.59], 0.2007	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0916		0.01 [-0.04, 0.07], 0.6207		-0.04 [-0.11, 0.03], 0.2590	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_3_m_pt_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.3.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.8538		0.9083		0.7206	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	6/40 (15.0)	2/70 (2.9)	1/36 (2.8)	6/138 (4.3)	7/76 (9.2)
RR [95%-CI]; p-value	0.39 [0.12, 1.31], 0.1273		1.03 [0.10, 10.97], 0.9814		0.47 [0.16, 1.35], 0.1627	
OR [95%-CI]; p-value	0.35 [0.09, 1.34], 0.1144		1.03 [0.09, 11.75], 0.9814		0.45 [0.14, 1.39], 0.1541	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1495		0.00 [-0.07, 0.07], 0.9813		-0.05 [-0.12, 0.02], 0.1940	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	4/32 (12.5)	5/74 (6.8)	2/36 (5.6)	8/147 (5.4)	6/68 (8.8)
RR [95%-CI]; p-value	0.33 [0.08, 1.39], 0.1295		1.22 [0.25, 5.97], 0.8094		0.62 [0.22, 1.71], 0.3525	
OR [95%-CI]; p-value	0.30 [0.06, 1.43], 0.1126		1.23 [0.23, 6.68], 0.8087		0.59 [0.20, 1.79], 0.3501	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1823		0.01 [-0.08, 0.11], 0.8026		-0.03 [-0.11, 0.04], 0.3878	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_3_m_pt_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.8.1.1.s9
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.7329		0.8770		0.9833	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	1/40 (2.5)	3/70 (4.3)	2/36 (5.6)	6/138 (4.3)	3/76 (3.9)
RR [95%-CI]; p-value	1.76 [0.19, 16.40], 0.6175		0.77 [0.13, 4.41], 0.7705		1.10 [0.28, 4.28], 0.8890	
OR [95%-CI]; p-value	1.80 [0.18, 17.91], 0.6114		0.76 [0.12, 4.77], 0.7702		1.11 [0.27, 4.55], 0.8889	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5856		-0.01 [-0.10, 0.08], 0.7788		0.00 [-0.05, 0.06], 0.8874	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	5/73 (6.8)	2/32 (6.3)	2/74 (2.7)	1/36 (2.8)	7/147 (4.8)	3/68 (4.4)
RR [95%-CI]; p-value	1.10 [0.22, 5.35], 0.9099		0.97 [0.09, 10.38], 0.9819		1.08 [0.29, 4.05], 0.9098	
OR [95%-CI]; p-value	1.10 [0.20, 6.01], 0.9098		0.97 [0.09, 11.09], 0.9819		1.08 [0.27, 4.32], 0.9097	
RD [95%-CI]; p-value	0.01 [-0.10, 0.11], 0.9083		-0.00 [-0.07, 0.06], 0.9820		0.00 [-0.06, 0.06], 0.9085	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_8_1_1_m_soc_sae5pct_bl25d.sas using SAS 9.4

Table 12.4.8.1.2.s9
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_8_1_2_m_pt_sae5pct_bl25d.sas using SAS 9.4

Table 12.4.5.1.1.s9
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_5_1_1_m_soc_aeg35pct_bl25d.sas using SAS 9.4

Table 12.4.5.1.2.s9
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_5_1_2_m_pt_aeg35pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1195		0.4984		0.1099	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	6/70 (8.6)	3/36 (8.3)	10/138 (7.2)	10/76 (13.2)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.03 [0.27, 3.87], 0.9668		0.55 [0.24, 1.26], 0.1593	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.03 [0.24, 4.39], 0.9668		0.52 [0.20, 1.30], 0.1551	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.00 [-0.11, 0.11], 0.9666		-0.06 [-0.15, 0.03], 0.1852	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	2/32 (6.3)	5/74 (6.8)	1/36 (2.8)	12/147 (8.2)	3/68 (4.4)
RR [95%-CI]; p-value	1.53 [0.34, 6.98], 0.5799		2.43 [0.29, 20.06], 0.4089		1.85 [0.54, 6.34], 0.3276	
OR [95%-CI]; p-value	1.59 [0.31, 8.12], 0.5737		2.54 [0.29, 22.55], 0.3885		1.93 [0.53, 7.06], 0.3153	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5434		0.04 [-0.04, 0.12], 0.3201		0.04 [-0.03, 0.10], 0.2645	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6434		0.4204		0.4477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	15/68 (22.1)	11/40 (27.5)	15/70 (21.4)	3/36 (8.3)	30/138 (21.7)	14/76 (18.4)
RR [95%-CI]; p-value	0.80 [0.41, 1.57], 0.5208		2.57 [0.80, 8.31], 0.1144		1.18 [0.67, 2.09], 0.5685	
OR [95%-CI]; p-value	0.75 [0.30, 1.84], 0.5230		3.00 [0.81, 11.15], 0.0890		1.23 [0.61, 2.49], 0.5655	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5302		0.13 [-0.00, 0.26], 0.0516		0.03 [-0.08, 0.14], 0.5581	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	13/73 (17.8)	9/32 (28.1)	11/74 (14.9)	4/36 (11.1)	24/147 (16.3)	13/68 (19.1)
RR [95%-CI]; p-value	0.63 [0.30, 1.33], 0.2270		1.34 [0.46, 3.91], 0.5949		0.85 [0.46, 1.57], 0.6125	
OR [95%-CI]; p-value	0.55 [0.21, 1.47], 0.2318		1.40 [0.41, 4.74], 0.5904		0.83 [0.39, 1.74], 0.6141	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2581		0.04 [-0.09, 0.17], 0.5738		-0.03 [-0.14, 0.08], 0.6219	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1769		0.7513		0.2112	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	9/68 (13.2)	5/40 (12.5)	10/70 (14.3)	6/36 (16.7)	19/138 (13.8)	11/76 (14.5)
RR [95%-CI]; p-value	1.06 [0.38, 2.94], 0.9126		0.86 [0.34, 2.17], 0.7450		0.95 [0.48, 1.89], 0.8867	
OR [95%-CI]; p-value	1.07 [0.33, 3.44], 0.9125		0.83 [0.28, 2.51], 0.7457		0.94 [0.42, 2.10], 0.8869	
RD [95%-CI]; p-value	0.01 [-0.12, 0.14], 0.9120		-0.02 [-0.17, 0.12], 0.7505		-0.01 [-0.10, 0.09], 0.8875	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	10/32 (31.3)	7/74 (9.5)	5/36 (13.9)	17/147 (11.6)	15/68 (22.1)
RR [95%-CI]; p-value	0.44 [0.20, 0.95], 0.0362		0.68 [0.23, 2.00], 0.4843		0.52 [0.28, 0.99], 0.0452	
OR [95%-CI]; p-value	0.35 [0.13, 0.95], 0.0350		0.65 [0.19, 2.20], 0.4844		0.46 [0.22, 0.99], 0.0444	
RD [95%-CI]; p-value	-0.18 [-0.35, 0.00], 0.0545		-0.04 [-0.18, 0.09], 0.5081		-0.10 [-0.22, 0.01], 0.0646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1286		0.1763		0.0462	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	23/68 (33.8)	10/40 (25.0)	20/70 (28.6)	7/36 (19.4)	43/138 (31.2)	17/76 (22.4)
RR [95%-CI]; p-value	1.35 [0.72, 2.54], 0.3481		1.47 [0.69, 3.15], 0.3217		1.39 [0.86, 2.27], 0.1820	
OR [95%-CI]; p-value	1.53 [0.64, 3.68], 0.3364		1.66 [0.63, 4.39], 0.3071		1.57 [0.82, 3.01], 0.1707	
RD [95%-CI]; p-value	0.09 [-0.09, 0.26], 0.3233		0.09 [-0.08, 0.26], 0.2843		0.09 [-0.03, 0.21], 0.1560	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	15/73 (20.5)	10/32 (31.3)	13/74 (17.6)	9/36 (25.0)	28/147 (19.0)	19/68 (27.9)
RR [95%-CI]; p-value	0.66 [0.33, 1.30], 0.2295		0.70 [0.33, 1.49], 0.3570		0.68 [0.41, 1.13], 0.1383	
OR [95%-CI]; p-value	0.57 [0.22, 1.45], 0.2359		0.64 [0.24, 1.67], 0.3605		0.61 [0.31, 1.19], 0.1423	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.08], 0.2580		-0.07 [-0.24, 0.09], 0.3799		-0.09 [-0.21, 0.04], 0.1602	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.2221		0.2372		0.0870	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	4/40 (10.0)	3/70 (4.3)	2/36 (5.6)	10/138 (7.2)	6/76 (7.9)
RR [95%-CI]; p-value	1.03 [0.32, 3.30], 0.9611		0.77 [0.13, 4.41], 0.7705		0.92 [0.35, 2.43], 0.8629	
OR [95%-CI]; p-value	1.03 [0.28, 3.77], 0.9611		0.76 [0.12, 4.77], 0.7702		0.91 [0.32, 2.61], 0.8630	
RD [95%-CI]; p-value	0.00 [-0.11, 0.12], 0.9609		-0.01 [-0.10, 0.08], 0.7788		-0.01 [-0.08, 0.07], 0.8645	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	1/32 (3.1)	8/74 (10.8)	1/36 (2.8)	18/147 (12.2)	2/68 (2.9)
RR [95%-CI]; p-value	4.38 [0.59, 32.82], 0.1502		3.89 [0.51, 29.94], 0.1918		4.16 [0.99, 17.44], 0.0510	
OR [95%-CI]; p-value	4.92 [0.60, 40.19], 0.1034		4.24 [0.51, 35.30], 0.1492		4.60 [1.04, 20.45], 0.0290	
RD [95%-CI]; p-value	0.11 [0.01, 0.21], 0.0368		0.08 [-0.01, 0.17], 0.0763		0.09 [0.03, 0.16], 0.0061	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5193		0.6986		0.5039	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	7/70 (10.0)	3/36 (8.3)	18/138 (13.0)	9/76 (11.8)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		1.20 [0.33, 4.37], 0.7820		1.10 [0.52, 2.33], 0.8005	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		1.22 [0.30, 5.04], 0.7810		1.12 [0.48, 2.62], 0.8000	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.02 [-0.10, 0.13], 0.7753		0.01 [-0.08, 0.10], 0.7976	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	4/32 (12.5)	7/74 (9.5)	4/36 (11.1)	13/147 (8.8)	8/68 (11.8)
RR [95%-CI]; p-value	0.66 [0.20, 2.17], 0.4917		0.85 [0.27, 2.72], 0.7861		0.75 [0.33, 1.73], 0.5016	
OR [95%-CI]; p-value	0.63 [0.16, 2.39], 0.4915		0.84 [0.23, 3.06], 0.7864		0.73 [0.29, 1.85], 0.5023	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5211		-0.02 [-0.14, 0.11], 0.7914		-0.03 [-0.12, 0.06], 0.5213	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.3592		0.7852		0.3259	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	18/68 (26.5)	17/40 (42.5)	14/70 (20.0)	8/36 (22.2)	32/138 (23.2)	25/76 (32.9)
RR [95%-CI]; p-value	0.62 [0.36, 1.06], 0.0832		0.90 [0.42, 1.94], 0.7886		0.70 [0.45, 1.10], 0.1210	
OR [95%-CI]; p-value	0.49 [0.21, 1.11], 0.0857		0.88 [0.33, 2.33], 0.7893		0.62 [0.33, 1.15], 0.1243	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.03], 0.0906		-0.02 [-0.19, 0.14], 0.7918		-0.10 [-0.22, 0.03], 0.1340	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	4/32 (12.5)	11/74 (14.9)	5/36 (13.9)	21/147 (14.3)	9/68 (13.2)
RR [95%-CI]; p-value	1.10 [0.37, 3.24], 0.8683		1.07 [0.40, 2.85], 0.8919		1.08 [0.52, 2.23], 0.8367	
OR [95%-CI]; p-value	1.11 [0.32, 3.85], 0.8679		1.08 [0.35, 3.39], 0.8916		1.09 [0.47, 2.53], 0.8362	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8659		0.01 [-0.13, 0.15], 0.8906		0.01 [-0.09, 0.11], 0.8343	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0583		0.3407		0.0358	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	15/40 (37.5)	9/70 (12.9)	8/36 (22.2)	17/138 (12.3)	23/76 (30.3)
RR [95%-CI]; p-value	0.31 [0.15, 0.67], 0.0029		0.58 [0.24, 1.37], 0.2142		0.41 [0.23, 0.71], 0.0017	
OR [95%-CI]; p-value	0.22 [0.08, 0.59], 0.0016		0.52 [0.18, 1.48], 0.2134		0.32 [0.16, 0.66], 0.0013	
RD [95%-CI]; p-value	-0.26 [-0.43, -0.09], 0.0027		-0.09 [-0.25, 0.06], 0.2418		-0.18 [-0.30, -0.06], 0.0026	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	16/73 (21.9)	8/32 (25.0)	13/74 (17.6)	6/36 (16.7)	29/147 (19.7)	14/68 (20.6)
RR [95%-CI]; p-value	0.88 [0.42, 1.84], 0.7275		1.05 [0.44, 2.55], 0.9068		0.96 [0.54, 1.69], 0.8832	
OR [95%-CI]; p-value	0.84 [0.32, 2.23], 0.7292		1.07 [0.37, 3.08], 0.9066		0.95 [0.46, 1.94], 0.8834	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7336		0.01 [-0.14, 0.16], 0.9060		-0.01 [-0.12, 0.11], 0.8841	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.4751		0.9511		0.8297	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	12/70 (17.1)	5/36 (13.9)	16/138 (11.6)	12/76 (15.8)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.23 [0.47, 3.23], 0.6683		0.73 [0.37, 1.47], 0.3832	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.28 [0.41, 3.97], 0.6655		0.70 [0.31, 1.57], 0.3838	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.03 [-0.11, 0.18], 0.6565		-0.04 [-0.14, 0.06], 0.4007	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	8/73 (11.0)	6/32 (18.8)	8/74 (10.8)	3/36 (8.3)	16/147 (10.9)	9/68 (13.2)
RR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2796		1.30 [0.37, 4.60], 0.6869		0.82 [0.38, 1.77], 0.6161	
OR [95%-CI]; p-value	0.53 [0.17, 1.69], 0.2797		1.33 [0.33, 5.36], 0.6844		0.80 [0.33, 1.92], 0.6170	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.08], 0.3184		0.02 [-0.09, 0.14], 0.6720		-0.02 [-0.12, 0.07], 0.6276	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.4623		0.9095		0.7196	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	6/68 (8.8)	4/40 (10.0)	7/70 (10.0)	4/36 (11.1)	13/138 (9.4)	8/76 (10.5)
RR [95%-CI]; p-value	0.88 [0.26, 2.94], 0.8385		0.90 [0.28, 2.87], 0.8588		0.89 [0.39, 2.06], 0.7944	
OR [95%-CI]; p-value	0.87 [0.23, 3.29], 0.8386		0.89 [0.24, 3.26], 0.8590		0.88 [0.35, 2.24], 0.7947	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.10], 0.8409		-0.01 [-0.14, 0.11], 0.8610		-0.01 [-0.10, 0.07], 0.7975	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	5/73 (6.8)	1/32 (3.1)	5/74 (6.8)	3/36 (8.3)	10/147 (6.8)	4/68 (5.9)
RR [95%-CI]; p-value	2.19 [0.27, 18.01], 0.4653		0.81 [0.21, 3.21], 0.7650		1.16 [0.38, 3.56], 0.7998	
OR [95%-CI]; p-value	2.28 [0.26, 20.34], 0.4492		0.80 [0.18, 3.54], 0.7651		1.17 [0.35, 3.87], 0.7992	
RD [95%-CI]; p-value	0.04 [-0.05, 0.12], 0.3827		-0.02 [-0.12, 0.09], 0.7725		0.01 [-0.06, 0.08], 0.7943	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.2828		0.2380		0.1477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	9/70 (12.9)	2/36 (5.6)	20/138 (14.5)	8/76 (10.5)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		2.31 [0.53, 10.15], 0.2660		1.38 [0.64, 2.98], 0.4161	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		2.51 [0.51, 12.28], 0.2431		1.44 [0.60, 3.45], 0.4103	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.07 [-0.04, 0.18], 0.1867		0.04 [-0.05, 0.13], 0.3909	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	6/32 (18.8)	8/74 (10.8)	5/36 (13.9)	15/147 (10.2)	11/68 (16.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.40], 0.1923		0.78 [0.27, 2.21], 0.6381		0.63 [0.31, 1.30], 0.2116	
OR [95%-CI]; p-value	0.46 [0.14, 1.50], 0.1895		0.75 [0.23, 2.49], 0.6389		0.59 [0.25, 1.36], 0.2117	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.06], 0.2349		-0.03 [-0.16, 0.10], 0.6508		-0.06 [-0.16, 0.04], 0.2431	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4122		0.5245		0.3607	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	5/68 (7.4)	4/40 (10.0)	7/70 (10.0)	2/36 (5.6)	12/138 (8.7)	6/76 (7.9)
RR [95%-CI]; p-value	0.74 [0.21, 2.58], 0.6312		1.80 [0.39, 8.22], 0.4483		1.10 [0.43, 2.82], 0.8402	
OR [95%-CI]; p-value	0.71 [0.18, 2.83], 0.6308		1.89 [0.37, 9.60], 0.4369		1.11 [0.40, 3.09], 0.8399	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.09], 0.6425		0.04 [-0.06, 0.15], 0.3961		0.01 [-0.07, 0.08], 0.8379	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	4/73 (5.5)	5/32 (15.6)	8/74 (10.8)	4/36 (11.1)	12/147 (8.2)	9/68 (13.2)
RR [95%-CI]; p-value	0.35 [0.10, 1.22], 0.0997		0.97 [0.31, 3.02], 0.9622		0.62 [0.27, 1.39], 0.2452	
OR [95%-CI]; p-value	0.31 [0.08, 1.25], 0.0874		0.97 [0.27, 3.46], 0.9622		0.58 [0.23, 1.46], 0.2440	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.03], 0.1443		-0.00 [-0.13, 0.12], 0.9623		-0.05 [-0.14, 0.04], 0.2794	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7480		0.7289		0.9661	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	6/40 (15.0)	7/70 (10.0)	4/36 (11.1)	15/138 (10.9)	10/76 (13.2)
RR [95%-CI]; p-value	0.78 [0.29, 2.10], 0.6284		0.90 [0.28, 2.87], 0.8588		0.83 [0.39, 1.75], 0.6174	
OR [95%-CI]; p-value	0.76 [0.24, 2.36], 0.6288		0.89 [0.24, 3.26], 0.8590		0.80 [0.34, 1.89], 0.6180	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.10], 0.6375		-0.01 [-0.14, 0.11], 0.8610		-0.02 [-0.11, 0.07], 0.6261	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	3/32 (9.4)	4/74 (5.4)	3/36 (8.3)	11/147 (7.5)	6/68 (8.8)
RR [95%-CI]; p-value	1.02 [0.28, 3.70], 0.9726		0.65 [0.15, 2.75], 0.5566		0.85 [0.33, 2.20], 0.7345	
OR [95%-CI]; p-value	1.03 [0.25, 4.25], 0.9726		0.63 [0.13, 2.97], 0.5550		0.84 [0.30, 2.36], 0.7348	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9725		-0.03 [-0.13, 0.07], 0.5809		-0.01 [-0.09, 0.07], 0.7417	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.4.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9649		0.7289		0.8279	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	7/40 (17.5)	4/70 (5.7)	0/36 (0.0)	7/138 (5.1)	7/76 (9.2)
RR [95%-CI]; p-value	0.25 [0.07, 0.92], 0.0370		4.17 [0.23, 76.77], 0.3365		0.55 [0.20, 1.51], 0.2468	
OR [95%-CI]; p-value	0.22 [0.05, 0.90], 0.0234		4.36 [0.22, 84.87], 0.2902		0.53 [0.18, 1.56], 0.2414	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.00], 0.0442		0.04 [-0.02, 0.11], 0.1982		-0.04 [-0.12, 0.03], 0.2770	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	5/32 (15.6)	2/74 (2.7)	0/36 (0.0)	5/147 (3.4)	5/68 (7.4)
RR [95%-CI]; p-value	0.26 [0.07, 1.03], 0.0560		1.97 [0.09, 42.65], 0.6648		0.46 [0.14, 1.54], 0.2102	
OR [95%-CI]; p-value	0.23 [0.05, 1.04], 0.0406		2.00 [0.09, 45.51], 0.6577		0.44 [0.12, 1.59], 0.2007	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0916		0.01 [-0.04, 0.07], 0.6207		-0.04 [-0.11, 0.03], 0.2590	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_4_m_pt_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.4.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.8538		0.9083		0.7206	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	6/40 (15.0)	2/70 (2.9)	1/36 (2.8)	6/138 (4.3)	7/76 (9.2)
RR [95%-CI]; p-value	0.39 [0.12, 1.31], 0.1273		1.03 [0.10, 10.97], 0.9814		0.47 [0.16, 1.35], 0.1627	
OR [95%-CI]; p-value	0.35 [0.09, 1.34], 0.1144		1.03 [0.09, 11.75], 0.9814		0.45 [0.14, 1.39], 0.1541	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1495		0.00 [-0.07, 0.07], 0.9813		-0.05 [-0.12, 0.02], 0.1940	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	4/32 (12.5)	5/74 (6.8)	2/36 (5.6)	8/147 (5.4)	6/68 (8.8)
RR [95%-CI]; p-value	0.33 [0.08, 1.39], 0.1295		1.22 [0.25, 5.97], 0.8094		0.62 [0.22, 1.71], 0.3525	
OR [95%-CI]; p-value	0.30 [0.06, 1.43], 0.1126		1.23 [0.23, 6.68], 0.8087		0.59 [0.20, 1.79], 0.3501	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1823		0.01 [-0.08, 0.11], 0.8026		-0.03 [-0.11, 0.04], 0.3878	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_4_m_pt_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.4.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.7853		0.6897		0.6912	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	6/68 (8.8)	3/40 (7.5)	6/70 (8.6)	4/36 (11.1)	12/138 (8.7)	7/76 (9.2)
RR [95%-CI]; p-value	1.18 [0.31, 4.45], 0.8107		0.77 [0.23, 2.56], 0.6716		0.94 [0.39, 2.30], 0.8991	
OR [95%-CI]; p-value	1.19 [0.28, 5.06], 0.8101		0.75 [0.20, 2.85], 0.6718		0.94 [0.35, 2.49], 0.8992	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.8064		-0.03 [-0.15, 0.10], 0.6828		-0.01 [-0.09, 0.08], 0.8999	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	4/73 (5.5)	2/32 (6.3)	2/74 (2.7)	2/36 (5.6)	6/147 (4.1)	4/68 (5.9)
RR [95%-CI]; p-value	0.88 [0.17, 4.55], 0.8755		0.49 [0.07, 3.32], 0.4618		0.69 [0.20, 2.38], 0.5610	
OR [95%-CI]; p-value	0.87 [0.15, 5.01], 0.8756		0.47 [0.06, 3.50], 0.4533		0.68 [0.19, 2.50], 0.5599	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8785		-0.03 [-0.11, 0.05], 0.5028		-0.02 [-0.08, 0.05], 0.5838	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_4_m_pt_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.4486		0.3000		0.8761	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	2/40 (5.0)	6/70 (8.6)	3/36 (8.3)	13/138 (9.4)	5/76 (6.6)
RR [95%-CI]; p-value	2.06 [0.45, 9.43], 0.3525		1.03 [0.27, 3.87], 0.9668		1.43 [0.53, 3.86], 0.4784	
OR [95%-CI]; p-value	2.18 [0.43, 11.05], 0.3364		1.03 [0.24, 4.39], 0.9668		1.48 [0.51, 4.31], 0.4736	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.2940		0.00 [-0.11, 0.11], 0.9666		0.03 [-0.05, 0.10], 0.4520	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	8/73 (11.0)	0/32 (0.0)	3/74 (4.1)	4/36 (11.1)	11/147 (7.5)	4/68 (5.9)
RR [95%-CI]; p-value	7.12 [0.42, 120.35], 0.1735		0.36 [0.09, 1.54], 0.1709		1.27 [0.42, 3.85], 0.6702	
OR [95%-CI]; p-value	7.88 [0.44, 141.49], 0.1007		0.34 [0.07, 1.60], 0.1548		1.29 [0.40, 4.22], 0.6683	
RD [95%-CI]; p-value	0.09 [0.01, 0.18], 0.0265		-0.07 [-0.18, 0.04], 0.2171		0.02 [-0.05, 0.09], 0.6552	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9048		0.9841		0.9369	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	1/68 (1.5)	0/40 (0.0)	1/70 (1.4)	1/36 (2.8)	2/138 (1.4)	1/76 (1.3)
RR [95%-CI]; p-value	1.19 [0.04, 34.72], 0.9190		0.51 [0.03, 7.98], 0.6346		1.10 [0.10, 11.95], 0.9367	
OR [95%-CI]; p-value	1.19 [0.04, 36.40], 0.9189		0.51 [0.03, 8.35], 0.6287		1.10 [0.10, 12.37], 0.9366	
RD [95%-CI]; p-value	0.00 [-0.04, 0.05], 0.9171		-0.01 [-0.07, 0.05], 0.6618		0.00 [-0.03, 0.03], 0.9358	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	1/73 (1.4)	0/32 (0.0)	0/74 (0.0)	0/36 (0.0)	1/147 (0.7)	0/68 (0.0)
RR [95%-CI]; p-value	0.89 [0.03, 25.88], 0.9462		NA		0.93 [0.03, 27.44], 0.9674	
OR [95%-CI]; p-value	0.89 [0.03, 27.18], 0.9462		NA		0.93 [0.03, 28.11], 0.9674	
RD [95%-CI]; p-value	-0.00 [-0.05, 0.05], 0.9473		NA		-0.00 [-0.02, 0.02], 0.9678	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4447		0.2502		0.7378	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	6/68 (8.8)	2/40 (5.0)	5/70 (7.1)	2/36 (5.6)	11/138 (8.0)	4/76 (5.3)
RR [95%-CI]; p-value	1.76 [0.37, 8.33], 0.4732		1.29 [0.26, 6.30], 0.7567		1.51 [0.50, 4.59], 0.4634	
OR [95%-CI]; p-value	1.84 [0.35, 9.58], 0.4638		1.31 [0.24, 7.10], 0.7553		1.56 [0.48, 5.08], 0.4578	
RD [95%-CI]; p-value	0.04 [-0.06, 0.13], 0.4323		0.02 [-0.08, 0.11], 0.7462		0.03 [-0.04, 0.09], 0.4320	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	0/32 (0.0)	3/74 (4.1)	4/36 (11.1)	10/147 (6.8)	4/68 (5.9)
RR [95%-CI]; p-value	6.23 [0.36, 106.59], 0.2065		0.36 [0.09, 1.54], 0.1709		1.16 [0.38, 3.56], 0.7998	
OR [95%-CI]; p-value	6.79 [0.37, 123.36], 0.1374		0.34 [0.07, 1.60], 0.1548		1.17 [0.35, 3.87], 0.7992	
RD [95%-CI]; p-value	0.08 [0.00, 0.16], 0.0477		-0.07 [-0.18, 0.04], 0.2171		0.01 [-0.06, 0.08], 0.7943	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.4840		0.7477		0.6121	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	2/68 (2.9)	1/40 (2.5)	2/70 (2.9)	0/36 (0.0)	4/138 (2.9)	1/76 (1.3)
RR [95%-CI]; p-value	1.18 [0.11, 12.57], 0.8930		2.09 [0.10, 45.07], 0.6392		2.20 [0.25, 19.36], 0.4763	
OR [95%-CI]; p-value	1.18 [0.10, 13.46], 0.8928		2.12 [0.09, 48.21], 0.6304		2.24 [0.25, 20.40], 0.4632	
RD [95%-CI]; p-value	0.00 [-0.06, 0.07], 0.8906		0.01 [-0.04, 0.07], 0.5912		0.02 [-0.02, 0.05], 0.4136	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	5/73 (6.8)	0/32 (0.0)	1/74 (1.4)	0/36 (0.0)	6/147 (4.1)	0/68 (0.0)
RR [95%-CI]; p-value	4.45 [0.25, 79.12], 0.3091		0.99 [0.03, 28.73], 0.9937		5.59 [0.32, 98.69], 0.2399	
OR [95%-CI]; p-value	4.71 [0.25, 88.78], 0.2572		0.99 [0.03, 30.09], 0.9937		5.79 [0.32, 105.12], 0.1804	
RD [95%-CI]; p-value	0.05 [-0.02, 0.12], 0.1468		-0.00 [-0.05, 0.05], 0.9937		0.03 [-0.00, 0.07], 0.0823	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7524		0.3726		0.6508	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	5/68 (7.4)	5/40 (12.5)	9/70 (12.9)	3/36 (8.3)	14/138 (10.1)	8/76 (10.5)
RR [95%-CI]; p-value	0.59 [0.18, 1.91], 0.3767		1.54 [0.45, 5.35], 0.4942		0.96 [0.42, 2.19], 0.9299	
OR [95%-CI]; p-value	0.56 [0.15, 2.05], 0.3729		1.62 [0.41, 6.41], 0.4863		0.96 [0.38, 2.40], 0.9299	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.07], 0.3998		0.05 [-0.07, 0.16], 0.4584		-0.00 [-0.09, 0.08], 0.9303	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	4/32 (12.5)	4/74 (5.4)	3/36 (8.3)	11/147 (7.5)	7/68 (10.3)
RR [95%-CI]; p-value	0.77 [0.24, 2.44], 0.6531		0.65 [0.15, 2.75], 0.5566		0.73 [0.29, 1.79], 0.4888	
OR [95%-CI]; p-value	0.74 [0.20, 2.74], 0.6539		0.63 [0.13, 2.97], 0.5550		0.70 [0.26, 1.91], 0.4889	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.10], 0.6680		-0.03 [-0.13, 0.07], 0.5809		-0.03 [-0.11, 0.06], 0.5110	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9048		0.3667		0.4157	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	1/68 (1.5)	0/40 (0.0)	3/70 (4.3)	0/36 (0.0)	4/138 (2.9)	0/76 (0.0)
RR [95%-CI]; p-value	1.19 [0.04, 34.72], 0.9190		3.13 [0.16, 60.80], 0.4512		4.43 [0.24, 82.77], 0.3185	
OR [95%-CI]; p-value	1.19 [0.04, 36.40], 0.9189		3.22 [0.16, 66.14], 0.4231		4.54 [0.24, 86.98], 0.2718	
RD [95%-CI]; p-value	0.00 [-0.04, 0.05], 0.9171		0.03 [-0.03, 0.09], 0.3457		0.02 [-0.01, 0.06], 0.1865	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	1/73 (1.4)	0/32 (0.0)	1/74 (1.4)	1/36 (2.8)	2/147 (1.4)	1/68 (1.5)
RR [95%-CI]; p-value	0.89 [0.03, 25.88], 0.9462		0.49 [0.03, 7.56], 0.6067		0.93 [0.09, 10.03], 0.9490	
OR [95%-CI]; p-value	0.89 [0.03, 27.18], 0.9462		0.48 [0.03, 7.89], 0.5993		0.92 [0.08, 10.37], 0.9490	
RD [95%-CI]; p-value	-0.00 [-0.05, 0.05], 0.9473		-0.01 [-0.07, 0.05], 0.6400		-0.00 [-0.04, 0.03], 0.9497	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7052		0.3804		0.7120	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	5/40 (12.5)	7/70 (10.0)	3/36 (8.3)	11/138 (8.0)	8/76 (10.5)
RR [95%-CI]; p-value	0.47 [0.13, 1.65], 0.2393		1.20 [0.33, 4.37], 0.7820		0.76 [0.32, 1.80], 0.5294	
OR [95%-CI]; p-value	0.44 [0.11, 1.74], 0.2295		1.22 [0.30, 5.04], 0.7810		0.74 [0.28, 1.92], 0.5294	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.05], 0.2666		0.02 [-0.10, 0.13], 0.7753		-0.03 [-0.11, 0.06], 0.5437	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	4/32 (12.5)	3/74 (4.1)	3/36 (8.3)	9/147 (6.1)	7/68 (10.3)
RR [95%-CI]; p-value	0.66 [0.20, 2.17], 0.4917		0.49 [0.10, 2.29], 0.3622		0.59 [0.23, 1.53], 0.2812	
OR [95%-CI]; p-value	0.63 [0.16, 2.39], 0.4915		0.46 [0.09, 2.43], 0.3537		0.57 [0.20, 1.60], 0.2784	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5211		-0.04 [-0.14, 0.06], 0.4056		-0.04 [-0.12, 0.04], 0.3185	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9581		0.5464		0.6334	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	2/68 (2.9)	0/40 (0.0)	3/70 (4.3)	0/36 (0.0)	5/138 (3.6)	0/76 (0.0)
RR [95%-CI]; p-value	2.38 [0.11, 51.55], 0.5800		3.13 [0.16, 60.80], 0.4512		5.54 [0.31, 100.11], 0.2460	
OR [95%-CI]; p-value	2.42 [0.11, 55.11], 0.5666		3.22 [0.16, 66.14], 0.4231		5.71 [0.31, 106.03], 0.1875	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5250		0.03 [-0.03, 0.09], 0.3457		0.03 [-0.01, 0.07], 0.1062	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	0/32 (0.0)	2/74 (2.7)	1/36 (2.8)	5/147 (3.4)	1/68 (1.5)
RR [95%-CI]; p-value	2.67 [0.14, 51.82], 0.5161		0.97 [0.09, 10.38], 0.9819		2.31 [0.28, 19.42], 0.4399	
OR [95%-CI]; p-value	2.74 [0.13, 56.37], 0.4960		0.97 [0.09, 11.09], 0.9819		2.36 [0.27, 20.59], 0.4241	
RD [95%-CI]; p-value	0.03 [-0.04, 0.09], 0.4176		-0.00 [-0.07, 0.06], 0.9820		0.02 [-0.02, 0.06], 0.3555	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.6.s9
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.5939		0.5609		0.3402	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	12/68 (17.6)	9/40 (22.5)	18/70 (25.7)	5/36 (13.9)	30/138 (21.7)	14/76 (18.4)
RR [95%-CI]; p-value	0.78 [0.36, 1.70], 0.5368		1.85 [0.75, 4.58], 0.1825		1.18 [0.67, 2.09], 0.5685	
OR [95%-CI]; p-value	0.74 [0.28, 1.95], 0.5383		2.15 [0.72, 6.36], 0.1619		1.23 [0.61, 2.49], 0.5655	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5471		0.12 [-0.03, 0.27], 0.1285		0.03 [-0.08, 0.14], 0.5581	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	12/73 (16.4)	9/32 (28.1)	10/74 (13.5)	4/36 (11.1)	22/147 (15.0)	13/68 (19.1)
RR [95%-CI]; p-value	0.58 [0.27, 1.25], 0.1648		1.22 [0.41, 3.61], 0.7246		0.78 [0.42, 1.46], 0.4408	
OR [95%-CI]; p-value	0.50 [0.19, 1.35], 0.1682		1.25 [0.36, 4.30], 0.7228		0.74 [0.35, 1.58], 0.4432	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1968		0.02 [-0.10, 0.15], 0.7148		-0.04 [-0.15, 0.07], 0.4587	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_6_m_pt_adr_bl25d.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalysen zu den Sicherheitsendpunkten (Unerwünschte Ereignisse (PP-Population))

Folgende Daten werden für die PP-Population:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (akutes Nierenversagen, Herzerkrankung
  - UE ohne erkrankungsbezogene Ereignisse
  - UE nach SOC und PT, die zum Abbruch führten

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.7432		0.8365		0.6389	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	37/51 (72.5)	22/28 (78.6)	25/40 (62.5)	16/26 (61.5)	62/91 (68.1)	38/54 (70.4)
RR [95%-CI]; p-value	0.92 [0.71, 1.19], 0.5427		1.02 [0.69, 1.50], 0.9375		0.97 [0.77, 1.21], 0.7762	
OR [95%-CI]; p-value	0.72 [0.24, 2.15], 0.5560		1.04 [0.38, 2.88], 0.9373		0.90 [0.43, 1.87], 0.7782	
RD [95%-CI]; p-value	-0.06 [-0.26, 0.13], 0.5454		0.01 [-0.23, 0.25], 0.9373		-0.02 [-0.18, 0.13], 0.7770	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	46/64 (71.9)	28/34 (82.4)	47/79 (59.5)	21/34 (61.8)	93/143 (65.0)	49/68 (72.1)
RR [95%-CI]; p-value	0.87 [0.70, 1.09], 0.2220		0.96 [0.70, 1.33], 0.8191		0.90 [0.75, 1.09], 0.2917	
OR [95%-CI]; p-value	0.55 [0.19, 1.54], 0.2509		0.91 [0.40, 2.07], 0.8211		0.72 [0.38, 1.36], 0.3094	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.06], 0.2242		-0.02 [-0.22, 0.17], 0.8203		-0.07 [-0.20, 0.06], 0.2978	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.5055		0.8620		0.6871	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	6/28 (21.4)	6/40 (15.0)	1/26 (3.8)	12/91 (13.2)	7/54 (13.0)
RR [95%-CI]; p-value	0.55 [0.20, 1.54], 0.2554		3.90 [0.50, 30.56], 0.1951		1.02 [0.43, 2.43], 0.9692	
OR [95%-CI]; p-value	0.49 [0.14, 1.69], 0.2523		4.41 [0.50, 38.99], 0.1505		1.02 [0.38, 2.77], 0.9692	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.08], 0.2814		0.11 [-0.02, 0.24], 0.1004		0.00 [-0.11, 0.12], 0.9691	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	4/34 (11.8)	7/79 (8.9)	1/34 (2.9)	14/143 (9.8)	5/68 (7.4)
RR [95%-CI]; p-value	0.93 [0.29, 2.95], 0.9016		3.01 [0.39, 23.55], 0.2932		1.33 [0.50, 3.55], 0.5667	
OR [95%-CI]; p-value	0.92 [0.25, 3.40], 0.9017		3.21 [0.38, 27.14], 0.2605		1.37 [0.47, 3.97], 0.5633	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.9027		0.06 [-0.03, 0.14], 0.1701		0.02 [-0.05, 0.10], 0.5447	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.3659		0.3114		0.2517	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	4/51 (7.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	6/91 (6.6)	2/54 (3.7)
RR [95%-CI]; p-value	4.47 [0.25, 81.57], 0.3122		0.65 [0.10, 4.33], 0.6562		1.78 [0.37, 8.51], 0.4700	
OR [95%-CI]; p-value	4.77 [0.24, 93.55], 0.2599		0.63 [0.08, 4.79], 0.6542		1.84 [0.36, 9.43], 0.4612	
RD [95%-CI]; p-value	0.06 [-0.03, 0.15], 0.1757		-0.03 [-0.15, 0.10], 0.6671		0.03 [-0.04, 0.10], 0.4294	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	8/64 (12.5)	4/34 (11.8)	1/79 (1.3)	3/34 (8.8)	9/143 (6.3)	7/68 (10.3)
RR [95%-CI]; p-value	1.06 [0.34, 3.28], 0.9159		0.14 [0.02, 1.33], 0.0875		0.61 [0.24, 1.57], 0.3073	
OR [95%-CI]; p-value	1.07 [0.30, 3.85], 0.9158		0.13 [0.01, 1.32], 0.0461		0.59 [0.21, 1.64], 0.3050	
RD [95%-CI]; p-value	0.01 [-0.13, 0.14], 0.9151		-0.08 [-0.17, 0.02], 0.1325		-0.04 [-0.12, 0.04], 0.3417	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.2364		0.8151		0.4394	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	8/51 (15.7)	2/28 (7.1)	5/40 (12.5)	4/26 (15.4)	13/91 (14.3)	6/54 (11.1)
RR [95%-CI]; p-value	2.20 [0.50, 9.64], 0.2973		0.81 [0.24, 2.75], 0.7384		1.29 [0.52, 3.18], 0.5870	
OR [95%-CI]; p-value	2.42 [0.48, 12.27], 0.2747		0.79 [0.19, 3.25], 0.7386		1.33 [0.48, 3.74], 0.5839	
RD [95%-CI]; p-value	0.09 [-0.05, 0.22], 0.2252		-0.03 [-0.20, 0.14], 0.7430		0.03 [-0.08, 0.14], 0.5731	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	12/64 (18.8)	8/34 (23.5)	7/79 (8.9)	3/34 (8.8)	19/143 (13.3)	11/68 (16.2)
RR [95%-CI]; p-value	0.80 [0.36, 1.76], 0.5742		1.00 [0.28, 3.65], 0.9949		0.82 [0.41, 1.63], 0.5729	
OR [95%-CI]; p-value	0.75 [0.27, 2.06], 0.5763		1.00 [0.24, 4.14], 0.9949		0.79 [0.35, 1.78], 0.5743	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5853		0.00 [-0.11, 0.11], 0.9949		-0.03 [-0.13, 0.07], 0.5850	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.7955		0.9959		0.9386	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	2/51 (3.9)	1/28 (3.6)	2/40 (5.0)	0/26 (0.0)	4/91 (4.4)	1/54 (1.9)
RR [95%-CI]; p-value	1.10 [0.10, 11.58], 0.9380		2.65 [0.12, 56.51], 0.5325		2.37 [0.27, 20.69], 0.4340	
OR [95%-CI]; p-value	1.10 [0.10, 12.72], 0.9379		2.74 [0.12, 63.16], 0.5135		2.44 [0.27, 22.39], 0.4170	
RD [95%-CI]; p-value	0.00 [-0.08, 0.09], 0.9371		0.03 [-0.05, 0.12], 0.4735		0.03 [-0.03, 0.08], 0.3680	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	2/34 (5.9)	3/79 (3.8)	0/34 (0.0)	9/143 (6.3)	2/68 (2.9)
RR [95%-CI]; p-value	1.59 [0.34, 7.47], 0.5544		2.62 [0.13, 50.92], 0.5246		2.14 [0.48, 9.64], 0.3217	
OR [95%-CI]; p-value	1.66 [0.32, 8.68], 0.5478		2.68 [0.13, 55.06], 0.5057		2.22 [0.47, 10.55], 0.3059	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5206		0.02 [-0.03, 0.08], 0.4277		0.03 [-0.02, 0.09], 0.2452	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9866		NA		0.9264	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	0/40 (0.0)	0/26 (0.0)	0/91 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	1/34 (2.9)	0/79 (0.0)	0/34 (0.0)	1/143 (0.7)	1/68 (1.5)
RR [95%-CI]; p-value	0.53 [0.03, 8.23], 0.6510		NA		0.48 [0.03, 7.49], 0.5972	
OR [95%-CI]; p-value	0.52 [0.03, 8.65], 0.6459		NA		0.47 [0.03, 7.66], 0.5889	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.6748		NA		-0.01 [-0.04, 0.02], 0.6335	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7777		NA		0.7266	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	0/40 (0.0)	0/26 (0.0)	0/91 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	0/64 (0.0)	1/34 (2.9)	0/79 (0.0)	0/34 (0.0)	0/143 (0.0)	1/68 (1.5)
RR [95%-CI]; p-value	0.26 [0.01, 7.66], 0.4379		NA		0.24 [0.01, 6.98], 0.4041	
OR [95%-CI]; p-value	0.26 [0.01, 7.89], 0.4040		NA		0.23 [0.01, 7.07], 0.3637	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.04], 0.4843		NA		-0.01 [-0.04, 0.02], 0.4663	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.4482		0.9978		0.5496	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	31/51 (60.8)	19/28 (67.9)	21/40 (52.5)	13/26 (50.0)	52/91 (57.1)	32/54 (59.3)
RR [95%-CI]; p-value	0.90 [0.64, 1.25], 0.5221		1.05 [0.65, 1.70], 0.8435		0.96 [0.73, 1.28], 0.8017	
OR [95%-CI]; p-value	0.73 [0.28, 1.94], 0.5327		1.11 [0.41, 2.97], 0.8426		0.92 [0.46, 1.82], 0.8029	
RD [95%-CI]; p-value	-0.07 [-0.29, 0.15], 0.5264		0.03 [-0.22, 0.27], 0.8426		-0.02 [-0.19, 0.14], 0.8025	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	37/64 (57.8)	26/34 (76.5)	39/79 (49.4)	16/34 (47.1)	76/143 (53.1)	42/68 (61.8)
RR [95%-CI]; p-value	0.76 [0.57, 1.00], 0.0505		1.05 [0.69, 1.60], 0.8235		0.86 [0.68, 1.10], 0.2239	
OR [95%-CI]; p-value	0.42 [0.17, 1.07], 0.0665		1.10 [0.49, 2.45], 0.8219		0.70 [0.39, 1.27], 0.2387	
RD [95%-CI]; p-value	-0.19 [-0.37, 0.00], 0.0505		0.02 [-0.18, 0.22], 0.8217		-0.09 [-0.23, 0.06], 0.2327	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.3057		0.5233		0.8247	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	14/51 (27.5)	12/28 (42.9)	15/40 (37.5)	7/26 (26.9)	29/91 (31.9)	19/54 (35.2)
RR [95%-CI]; p-value	0.64 [0.35, 1.19], 0.1578		1.39 [0.66, 2.95], 0.3859		0.91 [0.57, 1.45], 0.6799	
OR [95%-CI]; p-value	0.50 [0.19, 1.33], 0.1633		1.63 [0.55, 4.78], 0.3731		0.86 [0.42, 1.76], 0.6816	
RD [95%-CI]; p-value	-0.15 [-0.37, 0.07], 0.1708		0.11 [-0.12, 0.33], 0.3613		-0.03 [-0.19, 0.13], 0.6833	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	24/64 (37.5)	13/34 (38.2)	21/79 (26.6)	9/34 (26.5)	45/143 (31.5)	22/68 (32.4)
RR [95%-CI]; p-value	0.98 [0.58, 1.67], 0.9429		1.00 [0.51, 1.96], 0.9902		0.97 [0.64, 1.48], 0.8972	
OR [95%-CI]; p-value	0.97 [0.41, 2.28], 0.9430		1.01 [0.40, 2.50], 0.9902		0.96 [0.52, 1.78], 0.8974	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9431		0.00 [-0.18, 0.18], 0.9902		-0.01 [-0.14, 0.13], 0.8976	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.3659		0.3114		0.2517	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	4/51 (7.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	6/91 (6.6)	2/54 (3.7)
RR [95%-CI]; p-value	4.47 [0.25, 81.57], 0.3122		0.65 [0.10, 4.33], 0.6562		1.78 [0.37, 8.51], 0.4700	
OR [95%-CI]; p-value	4.77 [0.24, 93.55], 0.2599		0.63 [0.08, 4.79], 0.6542		1.84 [0.36, 9.43], 0.4612	
RD [95%-CI]; p-value	0.06 [-0.03, 0.15], 0.1757		-0.03 [-0.15, 0.10], 0.6671		0.03 [-0.04, 0.10], 0.4294	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	8/64 (12.5)	4/34 (11.8)	1/79 (1.3)	3/34 (8.8)	9/143 (6.3)	7/68 (10.3)
RR [95%-CI]; p-value	1.06 [0.34, 3.28], 0.9159		0.14 [0.02, 1.33], 0.0875		0.61 [0.24, 1.57], 0.3073	
OR [95%-CI]; p-value	1.07 [0.30, 3.85], 0.9158		0.13 [0.01, 1.32], 0.0461		0.59 [0.21, 1.64], 0.3050	
RD [95%-CI]; p-value	0.01 [-0.13, 0.14], 0.9151		-0.08 [-0.17, 0.02], 0.1325		-0.04 [-0.12, 0.04], 0.3417	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.0833		0.9891		0.1492	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	2/28 (7.1)	1/40 (2.5)	0/26 (0.0)	6/91 (6.6)	2/54 (3.7)
RR [95%-CI]; p-value	1.37 [0.28, 6.62], 0.6933		1.33 [0.05, 38.11], 0.8696		1.78 [0.37, 8.51], 0.4700	
OR [95%-CI]; p-value	1.41 [0.26, 7.80], 0.6905		1.33 [0.04, 41.20], 0.8690		1.84 [0.36, 9.43], 0.4612	
RD [95%-CI]; p-value	0.03 [-0.10, 0.15], 0.6778		0.01 [-0.06, 0.08], 0.8654		0.03 [-0.04, 0.10], 0.4294	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	7/34 (20.6)	6/79 (7.6)	2/34 (5.9)	9/143 (6.3)	9/68 (13.2)
RR [95%-CI]; p-value	0.23 [0.06, 0.82], 0.0242		1.29 [0.27, 6.08], 0.7465		0.48 [0.20, 1.14], 0.0969	
OR [95%-CI]; p-value	0.19 [0.05, 0.79], 0.0133		1.32 [0.25, 6.87], 0.7448		0.44 [0.17, 1.17], 0.0916	
RD [95%-CI]; p-value	-0.16 [-0.30, -0.01], 0.0321		0.02 [-0.08, 0.12], 0.7328		-0.07 [-0.16, 0.02], 0.1299	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.1383		0.1955		0.1489	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	9/28 (32.1)	10/40 (25.0)	5/26 (19.2)	16/91 (17.6)	14/54 (25.9)
RR [95%-CI]; p-value	0.37 [0.15, 0.92], 0.0331		1.30 [0.50, 3.37], 0.5896		0.68 [0.36, 1.28], 0.2295	
OR [95%-CI]; p-value	0.28 [0.09, 0.90], 0.0272		1.40 [0.42, 4.69], 0.5847		0.61 [0.27, 1.37], 0.2305	
RD [95%-CI]; p-value	-0.20 [-0.40, -0.01], 0.0398		0.06 [-0.14, 0.26], 0.5763		-0.08 [-0.22, 0.06], 0.2449	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	15/64 (23.4)	9/34 (26.5)	13/79 (16.5)	1/34 (2.9)	28/143 (19.6)	10/68 (14.7)
RR [95%-CI]; p-value	0.89 [0.43, 1.81], 0.7384		5.59 [0.76, 41.09], 0.0905		1.33 [0.69, 2.58], 0.3965	
OR [95%-CI]; p-value	0.85 [0.33, 2.21], 0.7396		6.50 [0.81, 51.84], 0.0455		1.41 [0.64, 3.11], 0.3892	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7426		0.14 [0.04, 0.23], 0.0078		0.05 [-0.06, 0.16], 0.3691	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.6494		0.8121		0.9156	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	8/51 (15.7)	7/28 (25.0)	4/40 (10.0)	3/26 (11.5)	12/91 (13.2)	10/54 (18.5)
RR [95%-CI]; p-value	0.63 [0.25, 1.55], 0.3120		0.87 [0.21, 3.56], 0.8427		0.71 [0.33, 1.54], 0.3866	
OR [95%-CI]; p-value	0.56 [0.18, 1.75], 0.3127		0.85 [0.17, 4.16], 0.8428		0.67 [0.27, 1.67], 0.3869	
RD [95%-CI]; p-value	-0.09 [-0.28, 0.10], 0.3339		-0.02 [-0.17, 0.14], 0.8448		-0.05 [-0.18, 0.07], 0.4023	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	8/34 (23.5)	10/79 (12.7)	4/34 (11.8)	17/143 (11.9)	12/68 (17.6)
RR [95%-CI]; p-value	0.46 [0.18, 1.17], 0.1046		1.08 [0.36, 3.19], 0.8950		0.67 [0.34, 1.33], 0.2550	
OR [95%-CI]; p-value	0.40 [0.13, 1.22], 0.0994		1.09 [0.32, 3.74], 0.8948		0.63 [0.28, 1.41], 0.2562	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1272		0.01 [-0.12, 0.14], 0.8935		-0.06 [-0.16, 0.05], 0.2824	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1524		0.8272		0.3768	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	14/51 (27.5)	11/28 (39.3)	12/40 (30.0)	7/26 (26.9)	26/91 (28.6)	18/54 (33.3)
RR [95%-CI]; p-value	0.70 [0.37, 1.33], 0.2732		1.11 [0.51, 2.46], 0.7885		0.86 [0.52, 1.41], 0.5439	
OR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2793		1.16 [0.39, 3.49], 0.7873		0.80 [0.39, 1.65], 0.5465	
RD [95%-CI]; p-value	-0.12 [-0.34, 0.10], 0.2883		0.03 [-0.19, 0.25], 0.7858		-0.05 [-0.20, 0.11], 0.5504	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	17/64 (26.6)	6/34 (17.6)	16/79 (20.3)	7/34 (20.6)	33/143 (23.1)	13/68 (19.1)
RR [95%-CI]; p-value	1.51 [0.65, 3.46], 0.3357		0.98 [0.45, 2.17], 0.9676		1.21 [0.68, 2.14], 0.5198	
OR [95%-CI]; p-value	1.69 [0.60, 4.78], 0.3216		0.98 [0.36, 2.65], 0.9676		1.27 [0.62, 2.60], 0.5151	
RD [95%-CI]; p-value	0.09 [-0.08, 0.26], 0.2975		-0.00 [-0.17, 0.16], 0.9677		0.04 [-0.08, 0.16], 0.5043	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0350		0.8073		0.0715	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	10/51 (19.6)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	14/91 (15.4)	5/54 (9.3)
RR [95%-CI]; p-value	1.83 [0.55, 6.11], 0.3256		1.30 [0.26, 6.60], 0.7515		1.66 [0.63, 4.36], 0.3019	
OR [95%-CI]; p-value	2.03 [0.51, 8.10], 0.3078		1.33 [0.23, 7.86], 0.7500		1.78 [0.60, 5.26], 0.2906	
RD [95%-CI]; p-value	0.09 [-0.07, 0.25], 0.2703		0.02 [-0.12, 0.16], 0.7437		0.06 [-0.05, 0.17], 0.2623	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	7/34 (20.6)	7/79 (8.9)	3/34 (8.8)	11/143 (7.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.30 [0.10, 0.96], 0.0432		1.00 [0.28, 3.65], 0.9949		0.52 [0.23, 1.17], 0.1152	
OR [95%-CI]; p-value	0.26 [0.07, 0.95], 0.0323		1.00 [0.24, 4.14], 0.9949		0.48 [0.19, 1.20], 0.1117	
RD [95%-CI]; p-value	-0.14 [-0.29, 0.00], 0.0581		0.00 [-0.11, 0.11], 0.9949		-0.07 [-0.16, 0.02], 0.1472	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8148		0.2299		0.2921	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	9/51 (17.6)	7/28 (25.0)	9/40 (22.5)	4/26 (15.4)	18/91 (19.8)	11/54 (20.4)
RR [95%-CI]; p-value	0.71 [0.29, 1.69], 0.4345		1.46 [0.50, 4.26], 0.4859		0.97 [0.50, 1.90], 0.9315	
OR [95%-CI]; p-value	0.64 [0.21, 1.97], 0.4366		1.60 [0.44, 5.85], 0.4776		0.96 [0.42, 2.23], 0.9316	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.12], 0.4517		0.07 [-0.12, 0.26], 0.4622		-0.01 [-0.14, 0.13], 0.9317	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	12/79 (15.2)	8/34 (23.5)	26/143 (18.2)	20/68 (29.4)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.65 [0.29, 1.44], 0.2832		0.62 [0.37, 1.03], 0.0627	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.58 [0.21, 1.59], 0.2867		0.53 [0.27, 1.05], 0.0648	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.08 [-0.25, 0.08], 0.3162		-0.11 [-0.24, 0.01], 0.0792	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4870		0.8860		0.5472	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	8/28 (28.6)	5/40 (12.5)	5/26 (19.2)	11/91 (12.1)	13/54 (24.1)
RR [95%-CI]; p-value	0.41 [0.16, 1.07], 0.0680		0.65 [0.21, 2.03], 0.4577		0.50 [0.24, 1.04], 0.0640	
OR [95%-CI]; p-value	0.33 [0.10, 1.09], 0.0613		0.60 [0.16, 2.32], 0.4562		0.43 [0.18, 1.05], 0.0604	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0818		-0.07 [-0.25, 0.12], 0.4707		-0.12 [-0.25, 0.01], 0.0757	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	15/79 (19.0)	9/34 (26.5)	29/143 (20.3)	21/68 (30.9)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.72 [0.35, 1.48], 0.3671		0.66 [0.41, 1.06], 0.0870	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.65 [0.25, 1.68], 0.3724		0.57 [0.30, 1.10], 0.0905	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.07 [-0.25, 0.10], 0.3929		-0.11 [-0.23, 0.02], 0.1047	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6767		0.9735		0.7728	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	6/28 (21.4)	6/40 (15.0)	4/26 (15.4)	11/91 (12.1)	10/54 (18.5)
RR [95%-CI]; p-value	0.46 [0.15, 1.37], 0.1611		0.98 [0.30, 3.13], 0.9660		0.65 [0.30, 1.43], 0.2883	
OR [95%-CI]; p-value	0.40 [0.11, 1.45], 0.1534		0.97 [0.25, 3.84], 0.9660		0.61 [0.24, 1.54], 0.2874	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1866		-0.00 [-0.18, 0.17], 0.9661		-0.06 [-0.19, 0.06], 0.3070	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	5/34 (14.7)	7/79 (8.9)	3/34 (8.8)	13/143 (9.1)	8/68 (11.8)
RR [95%-CI]; p-value	0.64 [0.21, 1.94], 0.4273		1.00 [0.28, 3.65], 0.9949		0.77 [0.34, 1.78], 0.5436	
OR [95%-CI]; p-value	0.60 [0.17, 2.13], 0.4262		1.00 [0.24, 4.14], 0.9949		0.75 [0.30, 1.91], 0.5443	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.09], 0.4517		0.00 [-0.11, 0.11], 0.9949		-0.03 [-0.12, 0.06], 0.5600	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.5637		0.7455		0.8072	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	3/28 (10.7)	3/40 (7.5)	2/26 (7.7)	4/91 (4.4)	5/54 (9.3)
RR [95%-CI]; p-value	0.18 [0.02, 1.68], 0.1330		0.98 [0.17, 5.44], 0.9770		0.47 [0.13, 1.69], 0.2506	
OR [95%-CI]; p-value	0.17 [0.02, 1.69], 0.0896		0.97 [0.15, 6.26], 0.9770		0.45 [0.12, 1.76], 0.2406	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1553		-0.00 [-0.13, 0.13], 0.9770		-0.05 [-0.14, 0.04], 0.2789	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	2/79 (2.5)	0/34 (0.0)	5/143 (3.5)	4/68 (5.9)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		1.75 [0.08, 37.75], 0.7220		0.59 [0.16, 2.14], 0.4267	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		1.77 [0.08, 40.21], 0.7178		0.58 [0.15, 2.23], 0.4228	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		0.01 [-0.04, 0.06], 0.6880		-0.02 [-0.09, 0.04], 0.4616	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5697		0.9948		0.7813	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	7/91 (7.7)	5/54 (9.3)
RR [95%-CI]; p-value	0.55 [0.12, 2.54], 0.4431		1.30 [0.26, 6.60], 0.7515		0.83 [0.28, 2.49], 0.7405	
OR [95%-CI]; p-value	0.52 [0.10, 2.77], 0.4381		1.33 [0.23, 7.86], 0.7500		0.82 [0.25, 2.71], 0.7406	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4714		0.02 [-0.12, 0.16], 0.7437		-0.02 [-0.11, 0.08], 0.7458	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	12/64 (18.8)	7/34 (20.6)	9/79 (11.4)	3/34 (8.8)	21/143 (14.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.91 [0.40, 2.10], 0.8261		1.29 [0.37, 4.48], 0.6871		1.00 [0.50, 2.00], 0.9969	
OR [95%-CI]; p-value	0.89 [0.31, 2.52], 0.8266		1.33 [0.34, 5.25], 0.6844		1.00 [0.44, 2.26], 0.9969	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.15], 0.8284		0.03 [-0.09, 0.14], 0.6704		-0.00 [-0.10, 0.10], 0.9969	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9746		0.9948		0.7928	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	4/28 (14.3)	3/40 (7.5)	2/26 (7.7)	6/91 (6.6)	6/54 (11.1)
RR [95%-CI]; p-value	0.41 [0.10, 1.71], 0.2220		0.98 [0.17, 5.44], 0.9770		0.59 [0.20, 1.75], 0.3437	
OR [95%-CI]; p-value	0.38 [0.08, 1.81], 0.2087		0.97 [0.15, 6.26], 0.9770		0.56 [0.17, 1.85], 0.3398	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2554		-0.00 [-0.13, 0.13], 0.9770		-0.05 [-0.14, 0.05], 0.3668	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	9/79 (11.4)	4/34 (11.8)	12/143 (8.4)	8/68 (11.8)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		0.97 [0.32, 2.93], 0.9546		0.71 [0.31, 1.66], 0.4342	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		0.96 [0.28, 3.38], 0.9546		0.69 [0.27, 1.77], 0.4344	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		-0.00 [-0.13, 0.13], 0.9549		-0.03 [-0.12, 0.06], 0.4578	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.3552		0.9073		0.5446	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	5/28 (17.9)	3/40 (7.5)	4/26 (15.4)	8/91 (8.8)	9/54 (16.7)
RR [95%-CI]; p-value	0.55 [0.17, 1.74], 0.3071		0.49 [0.12, 2.00], 0.3190		0.53 [0.22, 1.29], 0.1593	
OR [95%-CI]; p-value	0.50 [0.13, 1.90], 0.3031		0.45 [0.09, 2.18], 0.3094		0.48 [0.17, 1.34], 0.1541	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3348		-0.08 [-0.24, 0.08], 0.3369		-0.08 [-0.19, 0.04], 0.1802	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	3/34 (8.8)	3/79 (3.8)	3/34 (8.8)	10/143 (7.0)	6/68 (8.8)
RR [95%-CI]; p-value	1.24 [0.34, 4.49], 0.7436		0.43 [0.09, 2.03], 0.2861		0.79 [0.30, 2.09], 0.6385	
OR [95%-CI]; p-value	1.27 [0.31, 5.26], 0.7421		0.41 [0.08, 2.13], 0.2745		0.78 [0.27, 2.23], 0.6388	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7346		-0.05 [-0.15, 0.05], 0.3446		-0.02 [-0.10, 0.06], 0.6511	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.3.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.2640		0.8453		0.5363	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	7/28 (25.0)	3/40 (7.5)	0/26 (0.0)	4/91 (4.4)	7/54 (13.0)
RR [95%-CI]; p-value	0.08 [0.01, 0.61], 0.0146		3.98 [0.21, 76.20], 0.3598		0.34 [0.10, 1.11], 0.0728	
OR [95%-CI]; p-value	0.06 [0.01, 0.52], 0.0012		4.22 [0.20, 87.76], 0.3156		0.31 [0.09, 1.11], 0.0596	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.07], 0.0062		0.06 [-0.04, 0.15], 0.2551		-0.09 [-0.18, 0.01], 0.0898	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	5/34 (14.7)	3/79 (3.8)	0/34 (0.0)	6/143 (4.2)	5/68 (7.4)
RR [95%-CI]; p-value	0.32 [0.08, 1.25], 0.1018		2.62 [0.13, 50.92], 0.5246		0.57 [0.18, 1.80], 0.3395	
OR [95%-CI]; p-value	0.29 [0.06, 1.28], 0.0847		2.68 [0.13, 55.06], 0.5057		0.55 [0.16, 1.88], 0.3350	
RD [95%-CI]; p-value	-0.10 [-0.23, 0.03], 0.1304		0.02 [-0.03, 0.08], 0.4277		-0.03 [-0.10, 0.04], 0.3781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_3_m_pt_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.3.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2065		0.7544		0.1905	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	4/28 (14.3)	2/40 (5.0)	1/26 (3.8)	2/91 (2.2)	5/54 (9.3)
RR [95%-CI]; p-value	0.07 [0.00, 1.24], 0.0695		1.30 [0.12, 13.62], 0.8267		0.24 [0.05, 1.18], 0.0790	
OR [95%-CI]; p-value	0.06 [0.00, 1.16], 0.0141		1.32 [0.11, 15.29], 0.8260		0.22 [0.04, 1.18], 0.0551	
RD [95%-CI]; p-value	-0.13 [-0.27, -0.00], 0.0486		0.01 [-0.09, 0.11], 0.8213		-0.07 [-0.15, 0.01], 0.0953	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	4/34 (11.8)	5/79 (6.3)	1/34 (2.9)	9/143 (6.3)	5/68 (7.4)
RR [95%-CI]; p-value	0.53 [0.14, 1.99], 0.3484		2.15 [0.26, 17.73], 0.4764		0.86 [0.30, 2.46], 0.7725	
OR [95%-CI]; p-value	0.50 [0.12, 2.14], 0.3426		2.23 [0.25, 19.84], 0.4613		0.85 [0.27, 2.63], 0.7727	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.07], 0.3814		0.03 [-0.04, 0.11], 0.3955		-0.01 [-0.08, 0.06], 0.7782	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_3_m_pt_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.3.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.4182		0.8266		0.4723	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	4/51 (7.8)	3/28 (10.7)	2/40 (5.0)	4/26 (15.4)	6/91 (6.6)	7/54 (13.0)
RR [95%-CI]; p-value	0.73 [0.18, 3.04], 0.6677		0.33 [0.06, 1.65], 0.1750		0.51 [0.18, 1.43], 0.2014	
OR [95%-CI]; p-value	0.71 [0.15, 3.42], 0.6675		0.29 [0.05, 1.71], 0.1516		0.47 [0.15, 1.49], 0.1943	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.6796		-0.10 [-0.26, 0.05], 0.1870		-0.06 [-0.17, 0.04], 0.2259	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	1/34 (2.9)	2/79 (2.5)	2/34 (5.9)	6/143 (4.2)	3/68 (4.4)
RR [95%-CI]; p-value	2.13 [0.25, 18.27], 0.4923		0.43 [0.06, 2.93], 0.3890		0.95 [0.25, 3.69], 0.9421	
OR [95%-CI]; p-value	2.20 [0.24, 20.50], 0.4786		0.42 [0.06, 3.08], 0.3767		0.95 [0.23, 3.91], 0.9422	
RD [95%-CI]; p-value	0.03 [-0.05, 0.12], 0.4296		-0.03 [-0.12, 0.05], 0.4469		-0.00 [-0.06, 0.06], 0.9427	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_3_m_pt_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.8.1.1.s1.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.7369		0.1990		0.2218	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	0/28 (0.0)	0/40 (0.0)	3/26 (11.5)	1/91 (1.1)	3/54 (5.6)
RR [95%-CI]; p-value	1.12 [0.04, 32.29], 0.9483		0.11 [0.01, 2.05], 0.1380		0.20 [0.02, 1.85], 0.1558	
OR [95%-CI]; p-value	1.12 [0.04, 34.45], 0.9483		0.10 [0.00, 2.00], 0.0663		0.19 [0.02, 1.86], 0.1132	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9475		-0.10 [-0.23, 0.02], 0.1130		-0.04 [-0.11, 0.02], 0.1773	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	1/34 (2.9)	2/79 (2.5)	0/34 (0.0)	3/143 (2.1)	1/68 (1.5)
RR [95%-CI]; p-value	0.53 [0.03, 8.23], 0.6510		1.75 [0.08, 37.75], 0.7220		1.43 [0.15, 13.46], 0.7564	
OR [95%-CI]; p-value	0.52 [0.03, 8.65], 0.6459		1.77 [0.08, 40.21], 0.7178		1.44 [0.15, 14.06], 0.7548	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.6748		0.01 [-0.04, 0.06], 0.6880		0.01 [-0.03, 0.04], 0.7398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_8_1_1_m_soc_sae5pct_age_pp.sas using SAS 9.4

Table 12.4.8.1.2.s1.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_8_1_2_m_pt_sae5pct_age_pp.sas using SAS 9.4

Table 12.4.5.1.1.s1.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_5_1_1_m_soc_aeg35pct_age_pp.sas using SAS 9.4

Table 12.4.5.1.2.s1.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_5_1_2_m_pt_aeg35pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.1383		0.1955		0.1489	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	9/28 (32.1)	10/40 (25.0)	5/26 (19.2)	16/91 (17.6)	14/54 (25.9)
RR [95%-CI]; p-value	0.37 [0.15, 0.92], 0.0331		1.30 [0.50, 3.37], 0.5896		0.68 [0.36, 1.28], 0.2295	
OR [95%-CI]; p-value	0.28 [0.09, 0.90], 0.0272		1.40 [0.42, 4.69], 0.5847		0.61 [0.27, 1.37], 0.2305	
RD [95%-CI]; p-value	-0.20 [-0.40, -0.01], 0.0398		0.06 [-0.14, 0.26], 0.5763		-0.08 [-0.22, 0.06], 0.2449	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	15/64 (23.4)	9/34 (26.5)	13/79 (16.5)	1/34 (2.9)	28/143 (19.6)	10/68 (14.7)
RR [95%-CI]; p-value	0.89 [0.43, 1.81], 0.7384		5.59 [0.76, 41.09], 0.0905		1.33 [0.69, 2.58], 0.3965	
OR [95%-CI]; p-value	0.85 [0.33, 2.21], 0.7396		6.50 [0.81, 51.84], 0.0455		1.41 [0.64, 3.11], 0.3892	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7426		0.14 [0.04, 0.23], 0.0078		0.05 [-0.06, 0.16], 0.3691	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.6494		0.8121		0.9156	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	8/51 (15.7)	7/28 (25.0)	4/40 (10.0)	3/26 (11.5)	12/91 (13.2)	10/54 (18.5)
RR [95%-CI]; p-value	0.63 [0.25, 1.55], 0.3120		0.87 [0.21, 3.56], 0.8427		0.71 [0.33, 1.54], 0.3866	
OR [95%-CI]; p-value	0.56 [0.18, 1.75], 0.3127		0.85 [0.17, 4.16], 0.8428		0.67 [0.27, 1.67], 0.3869	
RD [95%-CI]; p-value	-0.09 [-0.28, 0.10], 0.3339		-0.02 [-0.17, 0.14], 0.8448		-0.05 [-0.18, 0.07], 0.4023	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	8/34 (23.5)	10/79 (12.7)	4/34 (11.8)	17/143 (11.9)	12/68 (17.6)
RR [95%-CI]; p-value	0.46 [0.18, 1.17], 0.1046		1.08 [0.36, 3.19], 0.8950		0.67 [0.34, 1.33], 0.2550	
OR [95%-CI]; p-value	0.40 [0.13, 1.22], 0.0994		1.09 [0.32, 3.74], 0.8948		0.63 [0.28, 1.41], 0.2562	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1272		0.01 [-0.12, 0.14], 0.8935		-0.06 [-0.16, 0.05], 0.2824	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1524		0.8272		0.3768	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	14/51 (27.5)	11/28 (39.3)	12/40 (30.0)	7/26 (26.9)	26/91 (28.6)	18/54 (33.3)
RR [95%-CI]; p-value	0.70 [0.37, 1.33], 0.2732		1.11 [0.51, 2.46], 0.7885		0.86 [0.52, 1.41], 0.5439	
OR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2793		1.16 [0.39, 3.49], 0.7873		0.80 [0.39, 1.65], 0.5465	
RD [95%-CI]; p-value	-0.12 [-0.34, 0.10], 0.2883		0.03 [-0.19, 0.25], 0.7858		-0.05 [-0.20, 0.11], 0.5504	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	17/64 (26.6)	6/34 (17.6)	16/79 (20.3)	7/34 (20.6)	33/143 (23.1)	13/68 (19.1)
RR [95%-CI]; p-value	1.51 [0.65, 3.46], 0.3357		0.98 [0.45, 2.17], 0.9676		1.21 [0.68, 2.14], 0.5198	
OR [95%-CI]; p-value	1.69 [0.60, 4.78], 0.3216		0.98 [0.36, 2.65], 0.9676		1.27 [0.62, 2.60], 0.5151	
RD [95%-CI]; p-value	0.09 [-0.08, 0.26], 0.2975		-0.00 [-0.17, 0.16], 0.9677		0.04 [-0.08, 0.16], 0.5043	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.8071		0.4451		0.3783	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	2/28 (7.1)	3/40 (7.5)	0/26 (0.0)	8/91 (8.8)	2/54 (3.7)
RR [95%-CI]; p-value	1.37 [0.28, 6.62], 0.6933		3.98 [0.21, 76.20], 0.3598		2.37 [0.52, 10.77], 0.2626	
OR [95%-CI]; p-value	1.41 [0.26, 7.80], 0.6905		4.22 [0.20, 87.76], 0.3156		2.51 [0.51, 12.26], 0.2425	
RD [95%-CI]; p-value	0.03 [-0.10, 0.15], 0.6778		0.06 [-0.04, 0.15], 0.2551		0.05 [-0.03, 0.13], 0.1951	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	3/34 (8.8)	5/79 (6.3)	2/34 (5.9)	11/143 (7.7)	5/68 (7.4)
RR [95%-CI]; p-value	1.06 [0.28, 3.99], 0.9284		1.08 [0.22, 5.28], 0.9281		1.05 [0.38, 2.89], 0.9307	
OR [95%-CI]; p-value	1.07 [0.25, 4.57], 0.9283		1.08 [0.20, 5.87], 0.9280		1.05 [0.35, 3.15], 0.9306	
RD [95%-CI]; p-value	0.01 [-0.11, 0.12], 0.9277		0.00 [-0.09, 0.10], 0.9270		0.00 [-0.07, 0.08], 0.9301	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0350		0.8073		0.0715	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	10/51 (19.6)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	14/91 (15.4)	5/54 (9.3)
RR [95%-CI]; p-value	1.83 [0.55, 6.11], 0.3256		1.30 [0.26, 6.60], 0.7515		1.66 [0.63, 4.36], 0.3019	
OR [95%-CI]; p-value	2.03 [0.51, 8.10], 0.3078		1.33 [0.23, 7.86], 0.7500		1.78 [0.60, 5.26], 0.2906	
RD [95%-CI]; p-value	0.09 [-0.07, 0.25], 0.2703		0.02 [-0.12, 0.16], 0.7437		0.06 [-0.05, 0.17], 0.2623	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	7/34 (20.6)	7/79 (8.9)	3/34 (8.8)	11/143 (7.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.30 [0.10, 0.96], 0.0432		1.00 [0.28, 3.65], 0.9949		0.52 [0.23, 1.17], 0.1152	
OR [95%-CI]; p-value	0.26 [0.07, 0.95], 0.0323		1.00 [0.24, 4.14], 0.9949		0.48 [0.19, 1.20], 0.1117	
RD [95%-CI]; p-value	-0.14 [-0.29, 0.00], 0.0581		0.00 [-0.11, 0.11], 0.9949		-0.07 [-0.16, 0.02], 0.1472	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8148		0.2299		0.2921	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	9/51 (17.6)	7/28 (25.0)	9/40 (22.5)	4/26 (15.4)	18/91 (19.8)	11/54 (20.4)
RR [95%-CI]; p-value	0.71 [0.29, 1.69], 0.4345		1.46 [0.50, 4.26], 0.4859		0.97 [0.50, 1.90], 0.9315	
OR [95%-CI]; p-value	0.64 [0.21, 1.97], 0.4366		1.60 [0.44, 5.85], 0.4776		0.96 [0.42, 2.23], 0.9316	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.12], 0.4517		0.07 [-0.12, 0.26], 0.4622		-0.01 [-0.14, 0.13], 0.9317	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	12/79 (15.2)	8/34 (23.5)	26/143 (18.2)	20/68 (29.4)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.65 [0.29, 1.44], 0.2832		0.62 [0.37, 1.03], 0.0627	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.58 [0.21, 1.59], 0.2867		0.53 [0.27, 1.05], 0.0648	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.08 [-0.25, 0.08], 0.3162		-0.11 [-0.24, 0.01], 0.0792	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4870		0.8860		0.5472	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	8/28 (28.6)	5/40 (12.5)	5/26 (19.2)	11/91 (12.1)	13/54 (24.1)
RR [95%-CI]; p-value	0.41 [0.16, 1.07], 0.0680		0.65 [0.21, 2.03], 0.4577		0.50 [0.24, 1.04], 0.0640	
OR [95%-CI]; p-value	0.33 [0.10, 1.09], 0.0613		0.60 [0.16, 2.32], 0.4562		0.43 [0.18, 1.05], 0.0604	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0818		-0.07 [-0.25, 0.12], 0.4707		-0.12 [-0.25, 0.01], 0.0757	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	15/79 (19.0)	9/34 (26.5)	29/143 (20.3)	21/68 (30.9)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.72 [0.35, 1.48], 0.3671		0.66 [0.41, 1.06], 0.0870	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.65 [0.25, 1.68], 0.3724		0.57 [0.30, 1.10], 0.0905	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.07 [-0.25, 0.10], 0.3929		-0.11 [-0.23, 0.02], 0.1047	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6767		0.9735		0.7728	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	6/28 (21.4)	6/40 (15.0)	4/26 (15.4)	11/91 (12.1)	10/54 (18.5)
RR [95%-CI]; p-value	0.46 [0.15, 1.37], 0.1611		0.98 [0.30, 3.13], 0.9660		0.65 [0.30, 1.43], 0.2883	
OR [95%-CI]; p-value	0.40 [0.11, 1.45], 0.1534		0.97 [0.25, 3.84], 0.9660		0.61 [0.24, 1.54], 0.2874	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1866		-0.00 [-0.18, 0.17], 0.9661		-0.06 [-0.19, 0.06], 0.3070	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	5/34 (14.7)	7/79 (8.9)	3/34 (8.8)	13/143 (9.1)	8/68 (11.8)
RR [95%-CI]; p-value	0.64 [0.21, 1.94], 0.4273		1.00 [0.28, 3.65], 0.9949		0.77 [0.34, 1.78], 0.5436	
OR [95%-CI]; p-value	0.60 [0.17, 2.13], 0.4262		1.00 [0.24, 4.14], 0.9949		0.75 [0.30, 1.91], 0.5443	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.09], 0.4517		0.00 [-0.11, 0.11], 0.9949		-0.03 [-0.12, 0.06], 0.5600	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5697		0.9948		0.7813	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	7/91 (7.7)	5/54 (9.3)
RR [95%-CI]; p-value	0.55 [0.12, 2.54], 0.4431		1.30 [0.26, 6.60], 0.7515		0.83 [0.28, 2.49], 0.7405	
OR [95%-CI]; p-value	0.52 [0.10, 2.77], 0.4381		1.33 [0.23, 7.86], 0.7500		0.82 [0.25, 2.71], 0.7406	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4714		0.02 [-0.12, 0.16], 0.7437		-0.02 [-0.11, 0.08], 0.7458	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	12/64 (18.8)	7/34 (20.6)	9/79 (11.4)	3/34 (8.8)	21/143 (14.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.91 [0.40, 2.10], 0.8261		1.29 [0.37, 4.48], 0.6871		1.00 [0.50, 2.00], 0.9969	
OR [95%-CI]; p-value	0.89 [0.31, 2.52], 0.8266		1.33 [0.34, 5.25], 0.6844		1.00 [0.44, 2.26], 0.9969	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.15], 0.8284		0.03 [-0.09, 0.14], 0.6704		-0.00 [-0.10, 0.10], 0.9969	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9746		0.9948		0.7928	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	4/28 (14.3)	3/40 (7.5)	2/26 (7.7)	6/91 (6.6)	6/54 (11.1)
RR [95%-CI]; p-value	0.41 [0.10, 1.71], 0.2220		0.98 [0.17, 5.44], 0.9770		0.59 [0.20, 1.75], 0.3437	
OR [95%-CI]; p-value	0.38 [0.08, 1.81], 0.2087		0.97 [0.15, 6.26], 0.9770		0.56 [0.17, 1.85], 0.3398	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2554		-0.00 [-0.13, 0.13], 0.9770		-0.05 [-0.14, 0.05], 0.3668	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	9/79 (11.4)	4/34 (11.8)	12/143 (8.4)	8/68 (11.8)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		0.97 [0.32, 2.93], 0.9546		0.71 [0.31, 1.66], 0.4342	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		0.96 [0.28, 3.38], 0.9546		0.69 [0.27, 1.77], 0.4344	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		-0.00 [-0.13, 0.13], 0.9549		-0.03 [-0.12, 0.06], 0.4578	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.3552		0.9073		0.5446	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	5/28 (17.9)	3/40 (7.5)	4/26 (15.4)	8/91 (8.8)	9/54 (16.7)
RR [95%-CI]; p-value	0.55 [0.17, 1.74], 0.3071		0.49 [0.12, 2.00], 0.3190		0.53 [0.22, 1.29], 0.1593	
OR [95%-CI]; p-value	0.50 [0.13, 1.90], 0.3031		0.45 [0.09, 2.18], 0.3094		0.48 [0.17, 1.34], 0.1541	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3348		-0.08 [-0.24, 0.08], 0.3369		-0.08 [-0.19, 0.04], 0.1802	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	3/34 (8.8)	3/79 (3.8)	3/34 (8.8)	10/143 (7.0)	6/68 (8.8)
RR [95%-CI]; p-value	1.24 [0.34, 4.49], 0.7436		0.43 [0.09, 2.03], 0.2861		0.79 [0.30, 2.09], 0.6385	
OR [95%-CI]; p-value	1.27 [0.31, 5.26], 0.7421		0.41 [0.08, 2.13], 0.2745		0.78 [0.27, 2.23], 0.6388	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7346		-0.05 [-0.15, 0.05], 0.3446		-0.02 [-0.10, 0.06], 0.6511	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.4.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.2640		0.8453		0.5363	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	7/28 (25.0)	3/40 (7.5)	0/26 (0.0)	4/91 (4.4)	7/54 (13.0)
RR [95%-CI]; p-value	0.08 [0.01, 0.61], 0.0146		3.98 [0.21, 76.20], 0.3598		0.34 [0.10, 1.11], 0.0728	
OR [95%-CI]; p-value	0.06 [0.01, 0.52], 0.0012		4.22 [0.20, 87.76], 0.3156		0.31 [0.09, 1.11], 0.0596	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.07], 0.0062		0.06 [-0.04, 0.15], 0.2551		-0.09 [-0.18, 0.01], 0.0898	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	5/34 (14.7)	3/79 (3.8)	0/34 (0.0)	6/143 (4.2)	5/68 (7.4)
RR [95%-CI]; p-value	0.32 [0.08, 1.25], 0.1018		2.62 [0.13, 50.92], 0.5246		0.57 [0.18, 1.80], 0.3395	
OR [95%-CI]; p-value	0.29 [0.06, 1.28], 0.0847		2.68 [0.13, 55.06], 0.5057		0.55 [0.16, 1.88], 0.3350	
RD [95%-CI]; p-value	-0.10 [-0.23, 0.03], 0.1304		0.02 [-0.03, 0.08], 0.4277		-0.03 [-0.10, 0.04], 0.3781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_4_m_pt_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.3303		0.9183		0.2782	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	8/91 (8.8)	2/54 (3.7)
RR [95%-CI]; p-value	6.71 [0.39, 115.74], 0.1904		0.65 [0.10, 4.33], 0.6562		2.37 [0.52, 10.77], 0.2626	
OR [95%-CI]; p-value	7.47 [0.40, 138.90], 0.1183		0.63 [0.08, 4.79], 0.6542		2.51 [0.51, 12.26], 0.2425	
RD [95%-CI]; p-value	0.10 [-0.00, 0.20], 0.0514		-0.03 [-0.15, 0.10], 0.6671		0.05 [-0.03, 0.13], 0.1951	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	5/64 (7.8)	2/34 (5.9)	4/79 (5.1)	3/34 (8.8)	9/143 (6.3)	5/68 (7.4)
RR [95%-CI]; p-value	1.33 [0.27, 6.49], 0.7259		0.57 [0.14, 2.43], 0.4503		0.86 [0.30, 2.46], 0.7725	
OR [95%-CI]; p-value	1.36 [0.25, 7.39], 0.7240		0.55 [0.12, 2.61], 0.4469		0.85 [0.27, 2.63], 0.7727	
RD [95%-CI]; p-value	0.02 [-0.08, 0.12], 0.7130		-0.04 [-0.14, 0.07], 0.4905		-0.01 [-0.08, 0.06], 0.7782	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7996		NA		0.8569	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	0/40 (0.0)	0/26 (0.0)	0/91 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	0/34 (0.0)	0/79 (0.0)	0/34 (0.0)	1/143 (0.7)	0/68 (0.0)
RR [95%-CI]; p-value	1.08 [0.04, 31.33], 0.9651		NA		0.96 [0.03, 28.21], 0.9802	
OR [95%-CI]; p-value	1.08 [0.04, 33.00], 0.9651		NA		0.96 [0.03, 28.90], 0.9802	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9647		NA		-0.00 [-0.02, 0.02], 0.9803	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2723		0.9183		0.2301	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	8/91 (8.8)	2/54 (3.7)
RR [95%-CI]; p-value	6.71 [0.39, 115.74], 0.1904		0.65 [0.10, 4.33], 0.6562		2.37 [0.52, 10.77], 0.2626	
OR [95%-CI]; p-value	7.47 [0.40, 138.90], 0.1183		0.63 [0.08, 4.79], 0.6542		2.51 [0.51, 12.26], 0.2425	
RD [95%-CI]; p-value	0.10 [-0.00, 0.20], 0.0514		-0.03 [-0.15, 0.10], 0.6671		0.05 [-0.03, 0.13], 0.1951	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	2/34 (5.9)	4/79 (5.1)	3/34 (8.8)	8/143 (5.6)	5/68 (7.4)
RR [95%-CI]; p-value	1.06 [0.20, 5.51], 0.9424		0.57 [0.14, 2.43], 0.4503		0.76 [0.26, 2.24], 0.6197	
OR [95%-CI]; p-value	1.07 [0.19, 6.14], 0.9424		0.55 [0.12, 2.61], 0.4469		0.75 [0.23, 2.37], 0.6195	
RD [95%-CI]; p-value	0.00 [-0.10, 0.10], 0.9419		-0.04 [-0.14, 0.07], 0.4905		-0.02 [-0.09, 0.05], 0.6349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8610		0.6708		0.6271	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	2/51 (3.9)	0/28 (0.0)	1/40 (2.5)	0/26 (0.0)	3/91 (3.3)	0/54 (0.0)
RR [95%-CI]; p-value	2.24 [0.10, 47.91], 0.6070		1.33 [0.05, 38.11], 0.8696		3.59 [0.18, 70.39], 0.3994	
OR [95%-CI]; p-value	2.29 [0.10, 52.47], 0.5954		1.33 [0.04, 41.20], 0.8690		3.68 [0.18, 74.92], 0.3646	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5544		0.01 [-0.06, 0.08], 0.8654		0.02 [-0.02, 0.07], 0.2954	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	1/34 (2.9)	0/79 (0.0)	0/34 (0.0)	3/143 (2.1)	1/68 (1.5)
RR [95%-CI]; p-value	1.59 [0.17, 14.74], 0.6813		NA		1.43 [0.15, 13.46], 0.7564	
OR [95%-CI]; p-value	1.62 [0.16, 16.23], 0.6775		NA		1.44 [0.15, 14.06], 0.7548	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6561		NA		0.01 [-0.03, 0.04], 0.7398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8058		0.3887		0.5479	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	5/28 (17.9)	3/40 (7.5)	1/26 (3.8)	9/91 (9.9)	6/54 (11.1)
RR [95%-CI]; p-value	0.66 [0.22, 1.97], 0.4545		1.95 [0.21, 17.75], 0.5534		0.89 [0.34, 2.36], 0.8153	
OR [95%-CI]; p-value	0.61 [0.17, 2.23], 0.4543		2.03 [0.20, 20.61], 0.5433		0.88 [0.29, 2.62], 0.8155	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4750		0.04 [-0.07, 0.15], 0.5155		-0.01 [-0.12, 0.09], 0.8178	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	4/34 (11.8)	6/79 (7.6)	4/34 (11.8)	10/143 (7.0)	8/68 (11.8)
RR [95%-CI]; p-value	0.53 [0.14, 1.99], 0.3484		0.65 [0.19, 2.14], 0.4746		0.59 [0.25, 1.44], 0.2486	
OR [95%-CI]; p-value	0.50 [0.12, 2.14], 0.3426		0.62 [0.16, 2.34], 0.4741		0.56 [0.21, 1.50], 0.2462	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.07], 0.3814		-0.04 [-0.16, 0.08], 0.5066		-0.05 [-0.13, 0.04], 0.2837	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.7996		0.6113		0.9129	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	1/40 (2.5)	0/26 (0.0)	1/91 (1.1)	0/54 (0.0)
RR [95%-CI]; p-value	NA		1.33 [0.05, 38.11], 0.8696		1.20 [0.04, 35.11], 0.9166	
OR [95%-CI]; p-value	NA		1.33 [0.04, 41.20], 0.8690		1.20 [0.04, 36.37], 0.9165	
RD [95%-CI]; p-value	NA		0.01 [-0.06, 0.08], 0.8654		0.00 [-0.03, 0.03], 0.9146	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	0/34 (0.0)	1/79 (1.3)	1/34 (2.9)	2/143 (1.4)	1/68 (1.5)
RR [95%-CI]; p-value	1.08 [0.04, 31.33], 0.9651		0.43 [0.03, 6.68], 0.5468		0.95 [0.09, 10.31], 0.9671	
OR [95%-CI]; p-value	1.08 [0.04, 33.00], 0.9651		0.42 [0.03, 6.97], 0.5356		0.95 [0.08, 10.67], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9647		-0.02 [-0.08, 0.05], 0.5959		-0.00 [-0.04, 0.03], 0.9674	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.5853		0.3201		0.3638	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	5/28 (17.9)	3/40 (7.5)	1/26 (3.8)	9/91 (9.9)	6/54 (11.1)
RR [95%-CI]; p-value	0.66 [0.22, 1.97], 0.4545		1.95 [0.21, 17.75], 0.5534		0.89 [0.34, 2.36], 0.8153	
OR [95%-CI]; p-value	0.61 [0.17, 2.23], 0.4543		2.03 [0.20, 20.61], 0.5433		0.88 [0.29, 2.62], 0.8155	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4750		0.04 [-0.07, 0.15], 0.5155		-0.01 [-0.12, 0.09], 0.8178	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	5/79 (6.3)	4/34 (11.8)	8/143 (5.6)	8/68 (11.8)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		0.54 [0.15, 1.88], 0.3317		0.48 [0.19, 1.21], 0.1198	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		0.51 [0.13, 2.02], 0.3277		0.44 [0.16, 1.24], 0.1136	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		-0.05 [-0.18, 0.07], 0.3781		-0.06 [-0.15, 0.02], 0.1565	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9870		0.8370		0.7350	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	2/51 (3.9)	0/28 (0.0)	1/40 (2.5)	0/26 (0.0)	3/91 (3.3)	0/54 (0.0)
RR [95%-CI]; p-value	2.24 [0.10, 47.91], 0.6070		1.33 [0.05, 38.11], 0.8696		3.59 [0.18, 70.39], 0.3994	
OR [95%-CI]; p-value	2.29 [0.10, 52.47], 0.5954		1.33 [0.04, 41.20], 0.8690		3.68 [0.18, 74.92], 0.3646	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5544		0.01 [-0.06, 0.08], 0.8654		0.02 [-0.02, 0.07], 0.2954	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	2/64 (3.1)	0/34 (0.0)	2/79 (2.5)	1/34 (2.9)	4/143 (2.8)	1/68 (1.5)
RR [95%-CI]; p-value	2.16 [0.10, 46.51], 0.6239		0.86 [0.08, 9.18], 0.9012		1.90 [0.22, 16.70], 0.5618	
OR [95%-CI]; p-value	2.19 [0.10, 50.03], 0.6139		0.86 [0.08, 9.78], 0.9012		1.93 [0.21, 17.59], 0.5538	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5737		-0.00 [-0.07, 0.06], 0.9040		0.01 [-0.03, 0.05], 0.5088	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.6.s1.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.0911		0.5003		0.1762	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	10/28 (35.7)	11/40 (27.5)	5/26 (19.2)	16/91 (17.6)	15/54 (27.8)
RR [95%-CI]; p-value	0.27 [0.10, 0.72], 0.0090		1.43 [0.56, 3.64], 0.4533		0.63 [0.34, 1.18], 0.1474	
OR [95%-CI]; p-value	0.20 [0.06, 0.65], 0.0050		1.59 [0.48, 5.27], 0.4437		0.55 [0.25, 1.24], 0.1477	
RD [95%-CI]; p-value	-0.26 [-0.45, -0.06], 0.0093		0.08 [-0.12, 0.29], 0.4296		-0.10 [-0.24, 0.04], 0.1617	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	11/64 (17.2)	7/34 (20.6)	12/79 (15.2)	2/34 (5.9)	23/143 (16.1)	9/68 (13.2)
RR [95%-CI]; p-value	0.83 [0.36, 1.96], 0.6777		2.58 [0.61, 10.92], 0.1972		1.22 [0.59, 2.48], 0.5928	
OR [95%-CI]; p-value	0.80 [0.28, 2.30], 0.6790		2.87 [0.61, 13.57], 0.1684		1.26 [0.55, 2.89], 0.5898	
RD [95%-CI]; p-value	-0.03 [-0.20, 0.13], 0.6851		0.09 [-0.02, 0.20], 0.1030		0.03 [-0.07, 0.13], 0.5788	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_6_m_pt_adr_age_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.2897		0.1542		0.0696	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	49/59 (83.1)	25/29 (86.2)	40/59 (67.8)	18/31 (58.1)	89/118 (75.4)	43/60 (71.7)
RR [95%-CI]; p-value	0.96 [0.80, 1.16], 0.6938		1.17 [0.83, 1.65], 0.3815		1.05 [0.87, 1.27], 0.5972	
OR [95%-CI]; p-value	0.78 [0.22, 2.75], 0.7036		1.52 [0.62, 3.73], 0.3594		1.21 [0.60, 2.44], 0.5883	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.13], 0.6951		0.10 [-0.11, 0.31], 0.3653		0.04 [-0.10, 0.18], 0.5935	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	34/56 (60.7)	25/33 (75.8)	32/60 (53.3)	19/29 (65.5)	66/116 (56.9)	44/62 (71.0)
RR [95%-CI]; p-value	0.80 [0.60, 1.07], 0.1289		0.81 [0.57, 1.16], 0.2554		0.80 [0.64, 1.00], 0.0538	
OR [95%-CI]; p-value	0.49 [0.19, 1.29], 0.1470		0.60 [0.24, 1.51], 0.2761		0.54 [0.28, 1.04], 0.0656	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.04], 0.1291		-0.12 [-0.34, 0.09], 0.2648		-0.14 [-0.29, 0.00], 0.0564	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.5846		0.5383		0.7579	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	7/59 (11.9)	6/29 (20.7)	5/59 (8.5)	0/31 (0.0)	12/118 (10.2)	6/60 (10.0)
RR [95%-CI]; p-value	0.57 [0.21, 1.55], 0.2737		5.34 [0.30, 94.61], 0.2534		1.02 [0.40, 2.58], 0.9717	
OR [95%-CI]; p-value	0.52 [0.16, 1.71], 0.2728		5.74 [0.30, 108.64], 0.1914		1.02 [0.36, 2.86], 0.9717	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.08], 0.3059		0.07 [-0.01, 0.15], 0.1055		0.00 [-0.09, 0.10], 0.9716	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	4/33 (12.1)	8/60 (13.3)	2/29 (6.9)	14/116 (12.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.88 [0.27, 2.90], 0.8389		1.93 [0.44, 8.53], 0.3842		1.25 [0.50, 3.08], 0.6326	
OR [95%-CI]; p-value	0.87 [0.23, 3.34], 0.8391		2.08 [0.41, 10.47], 0.3675		1.28 [0.47, 3.52], 0.6303	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.12], 0.8413		0.06 [-0.06, 0.19], 0.3171		0.02 [-0.07, 0.12], 0.6199	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.4637		0.8913		0.5475	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	1/29 (3.4)	1/59 (1.7)	2/31 (6.5)	7/118 (5.9)	3/60 (5.0)
RR [95%-CI]; p-value	2.95 [0.37, 23.37], 0.3058		0.26 [0.02, 2.78], 0.2671		1.19 [0.32, 4.43], 0.7991	
OR [95%-CI]; p-value	3.17 [0.36, 27.65], 0.2734		0.25 [0.02, 2.87], 0.2323		1.20 [0.30, 4.81], 0.7985	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1955		-0.05 [-0.14, 0.04], 0.3137		0.01 [-0.06, 0.08], 0.7932	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	3/33 (9.1)	2/60 (3.3)	3/29 (10.3)	8/116 (6.9)	6/62 (9.7)
RR [95%-CI]; p-value	1.18 [0.32, 4.40], 0.8069		0.32 [0.06, 1.82], 0.2004		0.71 [0.26, 1.96], 0.5120	
OR [95%-CI]; p-value	1.20 [0.28, 5.16], 0.8062		0.30 [0.05, 1.90], 0.1782		0.69 [0.23, 2.09], 0.5114	
RD [95%-CI]; p-value	0.02 [-0.11, 0.14], 0.8025		-0.07 [-0.19, 0.05], 0.2513		-0.03 [-0.11, 0.06], 0.5303	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.0994		0.7281		0.2424	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	11/59 (18.6)	2/29 (6.9)	4/59 (6.8)	3/31 (9.7)	15/118 (12.7)	5/60 (8.3)
RR [95%-CI]; p-value	2.70 [0.64, 11.41], 0.1757		0.70 [0.17, 2.93], 0.6263		1.53 [0.58, 4.00], 0.3902	
OR [95%-CI]; p-value	3.09 [0.64, 15.00], 0.1443		0.68 [0.14, 3.25], 0.6257		1.60 [0.55, 4.64], 0.3819	
RD [95%-CI]; p-value	0.12 [-0.02, 0.25], 0.0895		-0.03 [-0.15, 0.09], 0.6422		0.04 [-0.05, 0.14], 0.3520	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	8/33 (24.2)	8/60 (13.3)	4/29 (13.8)	17/116 (14.7)	12/62 (19.4)
RR [95%-CI]; p-value	0.66 [0.28, 1.55], 0.3430		0.97 [0.32, 2.95], 0.9525		0.76 [0.39, 1.48], 0.4169	
OR [95%-CI]; p-value	0.60 [0.21, 1.74], 0.3435		0.96 [0.26, 3.50], 0.9525		0.72 [0.32, 1.61], 0.4186	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.09], 0.3602		-0.00 [-0.16, 0.15], 0.9528		-0.05 [-0.16, 0.07], 0.4332	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.0699		0.8820		0.1018	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	3/29 (10.3)	2/59 (3.4)	0/31 (0.0)	4/118 (3.4)	3/60 (5.0)
RR [95%-CI]; p-value	0.33 [0.06, 1.85], 0.2070		2.14 [0.10, 45.94], 0.6279		0.68 [0.16, 2.93], 0.6029	
OR [95%-CI]; p-value	0.30 [0.05, 1.93], 0.1852		2.18 [0.10, 49.75], 0.6182		0.67 [0.14, 3.08], 0.6014	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2563		0.02 [-0.05, 0.08], 0.5782		-0.02 [-0.08, 0.05], 0.6224	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	0/33 (0.0)	3/60 (5.0)	0/29 (0.0)	9/116 (7.8)	0/62 (0.0)
RR [95%-CI]; p-value	7.18 [0.41, 124.48], 0.1757		2.95 [0.15, 57.00], 0.4740		9.70 [0.57, 164.52], 0.1158	
OR [95%-CI]; p-value	7.92 [0.43, 146.60], 0.1038		3.05 [0.15, 63.00], 0.4483		10.43 [0.59, 183.02], 0.0482	
RD [95%-CI]; p-value	0.09 [0.00, 0.18], 0.0466		0.03 [-0.04, 0.11], 0.3695		0.07 [0.02, 0.12], 0.0107	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.5125		NA		0.5527	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	1/29 (3.4)	0/59 (0.0)	0/31 (0.0)	0/118 (0.0)	1/60 (1.7)
RR [95%-CI]; p-value	0.24 [0.01, 7.06], 0.4110		NA		0.25 [0.01, 7.44], 0.4258	
OR [95%-CI]; p-value	0.24 [0.01, 7.29], 0.3723		NA		0.25 [0.01, 7.56], 0.3895	
RD [95%-CI]; p-value	-0.03 [-0.10, 0.04], 0.4674		NA		-0.01 [-0.05, 0.02], 0.4786	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	0/60 (0.0)	0/29 (0.0)	1/116 (0.9)	0/62 (0.0)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		NA		1.08 [0.04, 31.67], 0.9654	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		NA		1.08 [0.04, 32.59], 0.9654	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		NA		0.00 [-0.03, 0.03], 0.9650	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7350		NA		0.7758	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	1/29 (3.4)	0/59 (0.0)	0/31 (0.0)	0/118 (0.0)	1/60 (1.7)
RR [95%-CI]; p-value	0.24 [0.01, 7.06], 0.4110		NA		0.25 [0.01, 7.44], 0.4258	
OR [95%-CI]; p-value	0.24 [0.01, 7.29], 0.3723		NA		0.25 [0.01, 7.56], 0.3895	
RD [95%-CI]; p-value	-0.03 [-0.10, 0.04], 0.4674		NA		-0.01 [-0.05, 0.02], 0.4786	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	0/56 (0.0)	0/33 (0.0)	0/60 (0.0)	0/29 (0.0)	0/116 (0.0)	0/62 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.1009		0.3767		0.0847	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	44/59 (74.6)	23/29 (79.3)	32/59 (54.2)	14/31 (45.2)	76/118 (64.4)	37/60 (61.7)
RR [95%-CI]; p-value	0.94 [0.74, 1.19], 0.6126		1.20 [0.76, 1.89], 0.4284		1.04 [0.82, 1.33], 0.7230	
OR [95%-CI]; p-value	0.77 [0.26, 2.24], 0.6243		1.44 [0.60, 3.45], 0.4131		1.12 [0.59, 2.14], 0.7197	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.14], 0.6152		0.09 [-0.13, 0.31], 0.4112		0.03 [-0.12, 0.18], 0.7209	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	24/56 (42.9)	22/33 (66.7)	28/60 (46.7)	15/29 (51.7)	52/116 (44.8)	37/62 (59.7)
RR [95%-CI]; p-value	0.64 [0.44, 0.95], 0.0252		0.90 [0.58, 1.41], 0.6494		0.75 [0.56, 1.00], 0.0511	
OR [95%-CI]; p-value	0.38 [0.15, 0.92], 0.0299		0.82 [0.34, 1.98], 0.6545		0.55 [0.29, 1.03], 0.0590	
RD [95%-CI]; p-value	-0.24 [-0.44, -0.03], 0.0239		-0.05 [-0.27, 0.17], 0.6543		-0.15 [-0.30, 0.00], 0.0555	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.1886		0.0296		0.0091	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	19/59 (32.2)	8/29 (27.6)	23/59 (39.0)	6/31 (19.4)	42/118 (35.6)	14/60 (23.3)
RR [95%-CI]; p-value	1.17 [0.58, 2.34], 0.6631		2.01 [0.92, 4.42], 0.0809		1.53 [0.91, 2.56], 0.1107	
OR [95%-CI]; p-value	1.25 [0.47, 3.32], 0.6589		2.66 [0.95, 7.48], 0.0583		1.82 [0.90, 3.68], 0.0959	
RD [95%-CI]; p-value	0.05 [-0.16, 0.25], 0.6537		0.20 [0.01, 0.38], 0.0393		0.12 [-0.01, 0.26], 0.0806	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	19/56 (33.9)	17/33 (51.5)	13/60 (21.7)	10/29 (34.5)	32/116 (27.6)	27/62 (43.5)
RR [95%-CI]; p-value	0.66 [0.40, 1.08], 0.0969		0.63 [0.31, 1.26], 0.1901		0.63 [0.42, 0.95], 0.0287	
OR [95%-CI]; p-value	0.48 [0.20, 1.16], 0.1025		0.53 [0.20, 1.40], 0.1955		0.49 [0.26, 0.94], 0.0311	
RD [95%-CI]; p-value	-0.18 [-0.39, 0.03], 0.1021		-0.13 [-0.33, 0.07], 0.2136		-0.16 [-0.31, -0.01], 0.0343	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.4637		0.8913		0.5475	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	1/29 (3.4)	1/59 (1.7)	2/31 (6.5)	7/118 (5.9)	3/60 (5.0)
RR [95%-CI]; p-value	2.95 [0.37, 23.37], 0.3058		0.26 [0.02, 2.78], 0.2671		1.19 [0.32, 4.43], 0.7991	
OR [95%-CI]; p-value	3.17 [0.36, 27.65], 0.2734		0.25 [0.02, 2.87], 0.2323		1.20 [0.30, 4.81], 0.7985	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1955		-0.05 [-0.14, 0.04], 0.3137		0.01 [-0.06, 0.08], 0.7932	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	3/33 (9.1)	2/60 (3.3)	3/29 (10.3)	8/116 (6.9)	6/62 (9.7)
RR [95%-CI]; p-value	1.18 [0.32, 4.40], 0.8069		0.32 [0.06, 1.82], 0.2004		0.71 [0.26, 1.96], 0.5120	
OR [95%-CI]; p-value	1.20 [0.28, 5.16], 0.8062		0.30 [0.05, 1.90], 0.1782		0.69 [0.23, 2.09], 0.5114	
RD [95%-CI]; p-value	0.02 [-0.11, 0.14], 0.8025		-0.07 [-0.19, 0.05], 0.2513		-0.03 [-0.11, 0.06], 0.5303	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.5890		0.8138		0.3322	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	2/29 (6.9)	4/59 (6.8)	1/31 (3.2)	7/118 (5.9)	3/60 (5.0)
RR [95%-CI]; p-value	0.74 [0.13, 4.17], 0.7303		2.10 [0.25, 18.00], 0.4979		1.19 [0.32, 4.43], 0.7991	
OR [95%-CI]; p-value	0.72 [0.11, 4.59], 0.7300		2.18 [0.23, 20.41], 0.4843		1.20 [0.30, 4.81], 0.7985	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7421		0.04 [-0.05, 0.12], 0.4356		0.01 [-0.06, 0.08], 0.7932	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	7/33 (21.2)	3/60 (5.0)	1/29 (3.4)	8/116 (6.9)	8/62 (12.9)
RR [95%-CI]; p-value	0.42 [0.15, 1.22], 0.1109		1.45 [0.16, 13.34], 0.7428		0.53 [0.21, 1.35], 0.1869	
OR [95%-CI]; p-value	0.36 [0.11, 1.26], 0.1012		1.47 [0.15, 14.82], 0.7405		0.50 [0.18, 1.40], 0.1819	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1281		0.02 [-0.07, 0.10], 0.7246		-0.06 [-0.16, 0.04], 0.2169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.8363		0.6883		0.9003	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	10/29 (34.5)	13/59 (22.0)	3/31 (9.7)	25/118 (21.2)	13/60 (21.7)
RR [95%-CI]; p-value	0.59 [0.29, 1.20], 0.1461		2.28 [0.70, 7.39], 0.1709		0.98 [0.54, 1.77], 0.9410	
OR [95%-CI]; p-value	0.49 [0.18, 1.31], 0.1498		2.64 [0.69, 10.08], 0.1451		0.97 [0.46, 2.07], 0.9411	
RD [95%-CI]; p-value	-0.14 [-0.34, 0.06], 0.1682		0.12 [-0.02, 0.27], 0.1026		-0.00 [-0.13, 0.12], 0.9412	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	8/33 (24.2)	10/60 (16.7)	3/29 (10.3)	19/116 (16.4)	11/62 (17.7)
RR [95%-CI]; p-value	0.66 [0.28, 1.55], 0.3430		1.61 [0.48, 5.41], 0.4404		0.92 [0.47, 1.81], 0.8166	
OR [95%-CI]; p-value	0.60 [0.21, 1.74], 0.3435		1.73 [0.44, 6.85], 0.4287		0.91 [0.40, 2.05], 0.8170	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.09], 0.3602		0.06 [-0.08, 0.21], 0.3945		-0.01 [-0.13, 0.10], 0.8187	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8968		0.2880		0.4617	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	8/59 (13.6)	7/29 (24.1)	7/59 (11.9)	2/31 (6.5)	15/118 (12.7)	9/60 (15.0)
RR [95%-CI]; p-value	0.56 [0.23, 1.40], 0.2151		1.84 [0.41, 8.33], 0.4291		0.85 [0.39, 1.82], 0.6718	
OR [95%-CI]; p-value	0.49 [0.16, 1.53], 0.2148		1.95 [0.38, 10.02], 0.4160		0.83 [0.34, 2.01], 0.6726	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2456		0.05 [-0.07, 0.17], 0.3748		-0.02 [-0.13, 0.09], 0.6794	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	7/56 (12.5)	8/33 (24.2)	7/60 (11.7)	5/29 (17.2)	14/116 (12.1)	13/62 (21.0)
RR [95%-CI]; p-value	0.52 [0.21, 1.29], 0.1576		0.68 [0.23, 1.95], 0.4696		0.58 [0.29, 1.15], 0.1162	
OR [95%-CI]; p-value	0.45 [0.15, 1.37], 0.1529		0.63 [0.18, 2.20], 0.4705		0.52 [0.23, 1.18], 0.1148	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1757		-0.06 [-0.22, 0.10], 0.4938		-0.09 [-0.21, 0.03], 0.1374	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1251		0.8903		0.2081	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	22/59 (37.3)	8/29 (27.6)	18/59 (30.5)	9/31 (29.0)	40/118 (33.9)	17/60 (28.3)
RR [95%-CI]; p-value	1.35 [0.69, 2.66], 0.3824		1.05 [0.54, 2.06], 0.8849		1.20 [0.74, 1.92], 0.4591	
OR [95%-CI]; p-value	1.56 [0.59, 4.12], 0.3668		1.07 [0.41, 2.78], 0.8845		1.30 [0.66, 2.56], 0.4519	
RD [95%-CI]; p-value	0.10 [-0.11, 0.30], 0.3517		0.01 [-0.18, 0.21], 0.8840		0.06 [-0.09, 0.20], 0.4439	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	9/33 (27.3)	10/60 (16.7)	5/29 (17.2)	19/116 (16.4)	14/62 (22.6)
RR [95%-CI]; p-value	0.59 [0.26, 1.33], 0.2049		0.97 [0.36, 2.57], 0.9458		0.73 [0.39, 1.35], 0.3083	
OR [95%-CI]; p-value	0.51 [0.18, 1.45], 0.2038		0.96 [0.30, 3.12], 0.9459		0.67 [0.31, 1.45], 0.3104	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2222		-0.01 [-0.17, 0.16], 0.9461		-0.06 [-0.19, 0.06], 0.3269	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0634		0.7700		0.1043	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	10/59 (16.9)	3/29 (10.3)	5/59 (8.5)	2/31 (6.5)	15/118 (12.7)	5/60 (8.3)
RR [95%-CI]; p-value	1.64 [0.49, 5.50], 0.4243		1.31 [0.27, 6.38], 0.7353		1.53 [0.58, 4.00], 0.3902	
OR [95%-CI]; p-value	1.77 [0.45, 7.00], 0.4118		1.34 [0.25, 7.35], 0.7335		1.60 [0.55, 4.64], 0.3819	
RD [95%-CI]; p-value	0.07 [-0.08, 0.21], 0.3768		0.02 [-0.09, 0.13], 0.7232		0.04 [-0.05, 0.14], 0.3520	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	4/56 (7.1)	7/33 (21.2)	6/60 (10.0)	3/29 (10.3)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.34 [0.11, 1.06], 0.0637		0.97 [0.26, 3.59], 0.9596		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.29 [0.08, 1.06], 0.0514		0.96 [0.22, 4.16], 0.9597		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.14 [-0.30, 0.01], 0.0751		-0.00 [-0.14, 0.13], 0.9599		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0352		0.2680		0.3792	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	15/59 (25.4)	6/29 (20.7)	8/59 (13.6)	7/31 (22.6)	23/118 (19.5)	13/60 (21.7)
RR [95%-CI]; p-value	1.23 [0.53, 2.83], 0.6290		0.60 [0.24, 1.50], 0.2754		0.90 [0.49, 1.65], 0.7318	
OR [95%-CI]; p-value	1.31 [0.45, 3.82], 0.6243		0.54 [0.17, 1.66], 0.2752		0.88 [0.41, 1.88], 0.7327	
RD [95%-CI]; p-value	0.05 [-0.14, 0.23], 0.6152		-0.09 [-0.26, 0.08], 0.3016		-0.02 [-0.15, 0.10], 0.7359	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	13/33 (39.4)	13/60 (21.7)	5/29 (17.2)	21/116 (18.1)	18/62 (29.0)
RR [95%-CI]; p-value	0.36 [0.17, 0.78], 0.0097		1.26 [0.50, 3.19], 0.6306		0.62 [0.36, 1.08], 0.0917	
OR [95%-CI]; p-value	0.26 [0.09, 0.71], 0.0070		1.33 [0.42, 4.16], 0.6262		0.54 [0.26, 1.11], 0.0931	
RD [95%-CI]; p-value	-0.25 [-0.44, -0.06], 0.0097		0.04 [-0.13, 0.22], 0.6152		-0.11 [-0.24, 0.02], 0.1071	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.9665		0.0630		0.1769	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	11/29 (37.9)	14/59 (23.7)	6/31 (19.4)	26/118 (22.0)	17/60 (28.3)
RR [95%-CI]; p-value	0.54 [0.27, 1.07], 0.0753		1.23 [0.52, 2.87], 0.6392		0.78 [0.46, 1.32], 0.3492	
OR [95%-CI]; p-value	0.42 [0.16, 1.12], 0.0775		1.30 [0.44, 3.79], 0.6353		0.71 [0.35, 1.45], 0.3533	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.03], 0.0915		0.04 [-0.13, 0.22], 0.6270		-0.06 [-0.20, 0.07], 0.3652	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	9/33 (27.3)	6/60 (10.0)	8/29 (27.6)	14/116 (12.1)	17/62 (27.4)
RR [95%-CI]; p-value	0.52 [0.22, 1.23], 0.1358		0.36 [0.14, 0.95], 0.0385		0.44 [0.23, 0.83], 0.0115	
OR [95%-CI]; p-value	0.44 [0.15, 1.30], 0.1322		0.29 [0.09, 0.94], 0.0327		0.36 [0.16, 0.80], 0.0101	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1514		-0.18 [-0.36, 0.00], 0.0548		-0.15 [-0.28, -0.03], 0.0168	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8198		0.3494		0.6250	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	6/29 (20.7)	8/59 (13.6)	3/31 (9.7)	14/118 (11.9)	9/60 (15.0)
RR [95%-CI]; p-value	0.49 [0.17, 1.39], 0.1810		1.40 [0.40, 4.91], 0.5980		0.79 [0.36, 1.72], 0.5545	
OR [95%-CI]; p-value	0.43 [0.13, 1.49], 0.1765		1.46 [0.36, 5.97], 0.5932		0.76 [0.31, 1.88], 0.5555	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.06], 0.2153		0.04 [-0.10, 0.17], 0.5755		-0.03 [-0.14, 0.08], 0.5677	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	5/33 (15.2)	5/60 (8.3)	4/29 (13.8)	10/116 (8.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.59 [0.18, 1.88], 0.3726		0.60 [0.18, 2.08], 0.4249		0.59 [0.25, 1.38], 0.2274	
OR [95%-CI]; p-value	0.55 [0.15, 2.06], 0.3692		0.57 [0.14, 2.30], 0.4233		0.56 [0.21, 1.45], 0.2249	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.08], 0.3948		-0.05 [-0.20, 0.09], 0.4564		-0.06 [-0.16, 0.04], 0.2548	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3714		0.8456		0.6672	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	3/29 (10.3)	2/59 (3.4)	1/31 (3.2)	5/118 (4.2)	4/60 (6.7)
RR [95%-CI]; p-value	0.49 [0.11, 2.29], 0.3652		1.05 [0.10, 11.14], 0.9672		0.64 [0.18, 2.28], 0.4869	
OR [95%-CI]; p-value	0.46 [0.09, 2.46], 0.3575		1.05 [0.09, 12.09], 0.9671		0.62 [0.16, 2.40], 0.4844	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4065		0.00 [-0.08, 0.08], 0.9669		-0.02 [-0.10, 0.05], 0.5133	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	4/33 (12.1)	3/60 (5.0)	1/29 (3.4)	4/116 (3.4)	5/62 (8.1)
RR [95%-CI]; p-value	0.15 [0.02, 1.26], 0.0806		1.45 [0.16, 13.34], 0.7428		0.43 [0.12, 1.53], 0.1926	
OR [95%-CI]; p-value	0.13 [0.01, 1.23], 0.0408		1.47 [0.15, 14.82], 0.7405		0.41 [0.11, 1.58], 0.1805	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0824		0.02 [-0.07, 0.10], 0.7246		-0.05 [-0.12, 0.03], 0.2306	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.6761		0.2140		0.5381	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	7/59 (11.9)	5/29 (17.2)	9/59 (15.3)	2/31 (6.5)	16/118 (13.6)	7/60 (11.7)
RR [95%-CI]; p-value	0.69 [0.24, 1.98], 0.4887		2.36 [0.54, 10.28], 0.2510		1.16 [0.51, 2.67], 0.7232	
OR [95%-CI]; p-value	0.65 [0.19, 2.24], 0.4896		2.61 [0.53, 12.91], 0.2257		1.19 [0.46, 3.07], 0.7220	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5110		0.09 [-0.04, 0.21], 0.1712		0.02 [-0.08, 0.12], 0.7162	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	5/33 (15.2)	4/60 (6.7)	3/29 (10.3)	12/116 (10.3)	8/62 (12.9)
RR [95%-CI]; p-value	0.94 [0.34, 2.64], 0.9110		0.64 [0.15, 2.69], 0.5470		0.80 [0.35, 1.86], 0.6060	
OR [95%-CI]; p-value	0.93 [0.28, 3.13], 0.9111		0.62 [0.13, 2.97], 0.5457		0.78 [0.30, 2.02], 0.6066	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9116		-0.04 [-0.16, 0.09], 0.5719		-0.03 [-0.13, 0.07], 0.6167	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3473		0.0953		0.0572	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	4/59 (6.8)	3/29 (10.3)	6/59 (10.2)	0/31 (0.0)	10/118 (8.5)	3/60 (5.0)
RR [95%-CI]; p-value	0.66 [0.16, 2.74], 0.5623		6.41 [0.37, 111.02], 0.2019		1.69 [0.48, 5.93], 0.4089	
OR [95%-CI]; p-value	0.63 [0.13, 3.02], 0.5613		7.02 [0.38, 129.99], 0.1320		1.76 [0.47, 6.65], 0.3997	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.09], 0.5853		0.09 [-0.00, 0.17], 0.0577		0.03 [-0.04, 0.11], 0.3614	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	5/33 (15.2)	6/60 (10.0)	6/29 (20.7)	8/116 (6.9)	11/62 (17.7)
RR [95%-CI]; p-value	0.24 [0.05, 1.15], 0.0735		0.48 [0.17, 1.37], 0.1711		0.39 [0.16, 0.92], 0.0307	
OR [95%-CI]; p-value	0.21 [0.04, 1.14], 0.0500		0.43 [0.12, 1.46], 0.1664		0.34 [0.13, 0.91], 0.0256	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0847		-0.11 [-0.27, 0.06], 0.2064		-0.11 [-0.21, -0.00], 0.0443	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8323		0.3804		0.5422	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	4/29 (13.8)	2/59 (3.4)	1/31 (3.2)	8/118 (6.8)	5/60 (8.3)
RR [95%-CI]; p-value	0.74 [0.23, 2.41], 0.6140		1.05 [0.10, 11.14], 0.9672		0.81 [0.28, 2.38], 0.7063	
OR [95%-CI]; p-value	0.71 [0.18, 2.73], 0.6146		1.05 [0.09, 12.09], 0.9671		0.80 [0.25, 2.56], 0.7065	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6297		0.00 [-0.08, 0.08], 0.9669		-0.02 [-0.10, 0.07], 0.7149	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	4/33 (12.1)	4/60 (6.7)	6/29 (20.7)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.88 [0.27, 2.90], 0.8389		0.32 [0.10, 1.05], 0.0610		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.87 [0.23, 3.34], 0.8391		0.27 [0.07, 1.06], 0.0496		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.12], 0.8413		-0.14 [-0.30, 0.02], 0.0866		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.3.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4387		0.9692		0.3829	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	8/29 (27.6)	3/59 (5.1)	0/31 (0.0)	5/118 (4.2)	8/60 (13.3)
RR [95%-CI]; p-value	0.12 [0.03, 0.54], 0.0056		3.20 [0.17, 61.97], 0.4412		0.32 [0.11, 0.93], 0.0363	
OR [95%-CI]; p-value	0.09 [0.02, 0.47], 0.0008		3.32 [0.16, 68.46], 0.4111		0.29 [0.09, 0.92], 0.0275	
RD [95%-CI]; p-value	-0.24 [-0.41, -0.07], 0.0050		0.03 [-0.04, 0.11], 0.3346		-0.09 [-0.18, 0.00], 0.0562	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	4/33 (12.1)	3/60 (5.0)	0/29 (0.0)	5/116 (4.3)	4/62 (6.5)
RR [95%-CI]; p-value	0.29 [0.06, 1.52], 0.1447		2.95 [0.15, 57.00], 0.4740		0.67 [0.19, 2.40], 0.5363	
OR [95%-CI]; p-value	0.27 [0.05, 1.56], 0.1202		3.05 [0.15, 63.00], 0.4483		0.65 [0.17, 2.53], 0.5345	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1678		0.03 [-0.04, 0.11], 0.3695		-0.02 [-0.09, 0.05], 0.5570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_3_m_pt_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.3.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2827		0.5501		0.5543	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	3/29 (10.3)	4/59 (6.8)	2/31 (6.5)	7/118 (5.9)	5/60 (8.3)
RR [95%-CI]; p-value	0.49 [0.11, 2.29], 0.3652		1.05 [0.20, 5.42], 0.9528		0.71 [0.24, 2.15], 0.5465	
OR [95%-CI]; p-value	0.46 [0.09, 2.46], 0.3575		1.05 [0.18, 6.10], 0.9527		0.69 [0.21, 2.29], 0.5459	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4065		0.00 [-0.10, 0.11], 0.9524		-0.02 [-0.11, 0.06], 0.5655	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	5/33 (15.2)	3/60 (5.0)	0/29 (0.0)	4/116 (3.4)	5/62 (8.1)
RR [95%-CI]; p-value	0.12 [0.01, 0.97], 0.0463		2.95 [0.15, 57.00], 0.4740		0.43 [0.12, 1.53], 0.1926	
OR [95%-CI]; p-value	0.10 [0.01, 0.91], 0.0151		3.05 [0.15, 63.00], 0.4483		0.41 [0.11, 1.58], 0.1805	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.01], 0.0394		0.03 [-0.04, 0.11], 0.3695		-0.05 [-0.12, 0.03], 0.2306	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_3_m_pt_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.3.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.1779		0.7032		0.6951	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	3/29 (10.3)	1/59 (1.7)	1/31 (3.2)	4/118 (3.4)	4/60 (6.7)
RR [95%-CI]; p-value	0.49 [0.11, 2.29], 0.3652		0.53 [0.03, 8.12], 0.6450		0.51 [0.13, 1.96], 0.3264	
OR [95%-CI]; p-value	0.46 [0.09, 2.46], 0.3575		0.52 [0.03, 8.56], 0.6397		0.49 [0.12, 2.04], 0.3185	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4065		-0.02 [-0.09, 0.06], 0.6699		-0.03 [-0.10, 0.04], 0.3661	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	1/33 (3.0)	3/60 (5.0)	5/29 (17.2)	8/116 (6.9)	6/62 (9.7)
RR [95%-CI]; p-value	2.95 [0.36, 24.15], 0.3140		0.29 [0.07, 1.13], 0.0746		0.71 [0.26, 1.96], 0.5120	
OR [95%-CI]; p-value	3.14 [0.35, 28.09], 0.2838		0.25 [0.06, 1.14], 0.0584		0.69 [0.23, 2.09], 0.5114	
RD [95%-CI]; p-value	0.06 [-0.04, 0.15], 0.2230		-0.12 [-0.27, 0.03], 0.1053		-0.03 [-0.11, 0.06], 0.5303	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_3_m_pt_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.8.1.1.s2.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8112		0.7543		0.9754	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	1/59 (1.7)	0/29 (0.0)	0/59 (0.0)	1/31 (3.2)	1/118 (0.8)	1/60 (1.7)
RR [95%-CI]; p-value	1.00 [0.03, 28.96], 1.0000		0.26 [0.01, 7.55], 0.4336		0.51 [0.03, 7.99], 0.6303	
OR [95%-CI]; p-value	1.00 [0.03, 30.69], 1.0000		0.25 [0.01, 7.80], 0.3989		0.50 [0.03, 8.21], 0.6240	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 1.0000		-0.02 [-0.09, 0.04], 0.4812		-0.01 [-0.04, 0.03], 0.6589	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	1/33 (3.0)	2/60 (3.3)	2/29 (6.9)	3/116 (2.6)	3/62 (4.8)
RR [95%-CI]; p-value	0.59 [0.04, 9.11], 0.7050		0.48 [0.07, 3.26], 0.4554		0.53 [0.11, 2.57], 0.4343	
OR [95%-CI]; p-value	0.58 [0.04, 9.62], 0.7020		0.47 [0.06, 3.48], 0.4470		0.52 [0.10, 2.67], 0.4276	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.06], 0.7198		-0.04 [-0.14, 0.07], 0.4969		-0.02 [-0.08, 0.04], 0.4672	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_8_1_1_m_soc_sae5pct_sex_pp.sas using SAS 9.4

Table 12.4.8.1.2.s2.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_8_1_2_m_pt_sae5pct_sex_pp.sas using SAS 9.4

Table 12.4.5.1.1.s2.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_5_1_1_m_soc_aeg35pct_sex_pp.sas using SAS 9.4

Table 12.4.5.1.2.s2.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_5_1_2_m_pt_aeg35pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.8363		0.6883		0.9003	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	10/29 (34.5)	13/59 (22.0)	3/31 (9.7)	25/118 (21.2)	13/60 (21.7)
RR [95%-CI]; p-value	0.59 [0.29, 1.20], 0.1461		2.28 [0.70, 7.39], 0.1709		0.98 [0.54, 1.77], 0.9410	
OR [95%-CI]; p-value	0.49 [0.18, 1.31], 0.1498		2.64 [0.69, 10.08], 0.1451		0.97 [0.46, 2.07], 0.9411	
RD [95%-CI]; p-value	-0.14 [-0.34, 0.06], 0.1682		0.12 [-0.02, 0.27], 0.1026		-0.00 [-0.13, 0.12], 0.9412	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	8/33 (24.2)	10/60 (16.7)	3/29 (10.3)	19/116 (16.4)	11/62 (17.7)
RR [95%-CI]; p-value	0.66 [0.28, 1.55], 0.3430		1.61 [0.48, 5.41], 0.4404		0.92 [0.47, 1.81], 0.8166	
OR [95%-CI]; p-value	0.60 [0.21, 1.74], 0.3435		1.73 [0.44, 6.85], 0.4287		0.91 [0.40, 2.05], 0.8170	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.09], 0.3602		0.06 [-0.08, 0.21], 0.3945		-0.01 [-0.13, 0.10], 0.8187	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8968		0.2880		0.4617	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	8/59 (13.6)	7/29 (24.1)	7/59 (11.9)	2/31 (6.5)	15/118 (12.7)	9/60 (15.0)
RR [95%-CI]; p-value	0.56 [0.23, 1.40], 0.2151		1.84 [0.41, 8.33], 0.4291		0.85 [0.39, 1.82], 0.6718	
OR [95%-CI]; p-value	0.49 [0.16, 1.53], 0.2148		1.95 [0.38, 10.02], 0.4160		0.83 [0.34, 2.01], 0.6726	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2456		0.05 [-0.07, 0.17], 0.3748		-0.02 [-0.13, 0.09], 0.6794	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	7/56 (12.5)	8/33 (24.2)	7/60 (11.7)	5/29 (17.2)	14/116 (12.1)	13/62 (21.0)
RR [95%-CI]; p-value	0.52 [0.21, 1.29], 0.1576		0.68 [0.23, 1.95], 0.4696		0.58 [0.29, 1.15], 0.1162	
OR [95%-CI]; p-value	0.45 [0.15, 1.37], 0.1529		0.63 [0.18, 2.20], 0.4705		0.52 [0.23, 1.18], 0.1148	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1757		-0.06 [-0.22, 0.10], 0.4938		-0.09 [-0.21, 0.03], 0.1374	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1251		0.8903		0.2081	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	22/59 (37.3)	8/29 (27.6)	18/59 (30.5)	9/31 (29.0)	40/118 (33.9)	17/60 (28.3)
RR [95%-CI]; p-value	1.35 [0.69, 2.66], 0.3824		1.05 [0.54, 2.06], 0.8849		1.20 [0.74, 1.92], 0.4591	
OR [95%-CI]; p-value	1.56 [0.59, 4.12], 0.3668		1.07 [0.41, 2.78], 0.8845		1.30 [0.66, 2.56], 0.4519	
RD [95%-CI]; p-value	0.10 [-0.11, 0.30], 0.3517		0.01 [-0.18, 0.21], 0.8840		0.06 [-0.09, 0.20], 0.4439	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	9/33 (27.3)	10/60 (16.7)	5/29 (17.2)	19/116 (16.4)	14/62 (22.6)
RR [95%-CI]; p-value	0.59 [0.26, 1.33], 0.2049		0.97 [0.36, 2.57], 0.9458		0.73 [0.39, 1.35], 0.3083	
OR [95%-CI]; p-value	0.51 [0.18, 1.45], 0.2038		0.96 [0.30, 3.12], 0.9459		0.67 [0.31, 1.45], 0.3104	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2222		-0.01 [-0.17, 0.16], 0.9461		-0.06 [-0.19, 0.06], 0.3269	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.6998		0.4383		0.3536	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	3/29 (10.3)	4/59 (6.8)	2/31 (6.5)	10/118 (8.5)	5/60 (8.3)
RR [95%-CI]; p-value	0.98 [0.26, 3.65], 0.9796		1.05 [0.20, 5.42], 0.9528		1.02 [0.36, 2.84], 0.9744	
OR [95%-CI]; p-value	0.98 [0.23, 4.24], 0.9796		1.05 [0.18, 6.10], 0.9527		1.02 [0.33, 3.13], 0.9744	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9797		0.00 [-0.10, 0.11], 0.9524		0.00 [-0.08, 0.09], 0.9744	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	2/33 (6.1)	4/60 (6.7)	0/29 (0.0)	9/116 (7.8)	2/62 (3.2)
RR [95%-CI]; p-value	1.47 [0.30, 7.17], 0.6313		3.93 [0.21, 71.97], 0.3558		2.41 [0.54, 10.79], 0.2518	
OR [95%-CI]; p-value	1.52 [0.28, 8.31], 0.6273		4.14 [0.21, 81.07], 0.3116		2.52 [0.53, 12.06], 0.2315	
RD [95%-CI]; p-value	0.03 [-0.08, 0.14], 0.6109		0.05 [-0.03, 0.13], 0.2142		0.05 [-0.02, 0.11], 0.1757	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0634		0.7700		0.1043	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	10/59 (16.9)	3/29 (10.3)	5/59 (8.5)	2/31 (6.5)	15/118 (12.7)	5/60 (8.3)
RR [95%-CI]; p-value	1.64 [0.49, 5.50], 0.4243		1.31 [0.27, 6.38], 0.7353		1.53 [0.58, 4.00], 0.3902	
OR [95%-CI]; p-value	1.77 [0.45, 7.00], 0.4118		1.34 [0.25, 7.35], 0.7335		1.60 [0.55, 4.64], 0.3819	
RD [95%-CI]; p-value	0.07 [-0.08, 0.21], 0.3768		0.02 [-0.09, 0.13], 0.7232		0.04 [-0.05, 0.14], 0.3520	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	4/56 (7.1)	7/33 (21.2)	6/60 (10.0)	3/29 (10.3)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.34 [0.11, 1.06], 0.0637		0.97 [0.26, 3.59], 0.9596		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.29 [0.08, 1.06], 0.0514		0.96 [0.22, 4.16], 0.9597		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.14 [-0.30, 0.01], 0.0751		-0.00 [-0.14, 0.13], 0.9599		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0352		0.2680		0.3792	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	15/59 (25.4)	6/29 (20.7)	8/59 (13.6)	7/31 (22.6)	23/118 (19.5)	13/60 (21.7)
RR [95%-CI]; p-value	1.23 [0.53, 2.83], 0.6290		0.60 [0.24, 1.50], 0.2754		0.90 [0.49, 1.65], 0.7318	
OR [95%-CI]; p-value	1.31 [0.45, 3.82], 0.6243		0.54 [0.17, 1.66], 0.2752		0.88 [0.41, 1.88], 0.7327	
RD [95%-CI]; p-value	0.05 [-0.14, 0.23], 0.6152		-0.09 [-0.26, 0.08], 0.3016		-0.02 [-0.15, 0.10], 0.7359	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	13/33 (39.4)	13/60 (21.7)	5/29 (17.2)	21/116 (18.1)	18/62 (29.0)
RR [95%-CI]; p-value	0.36 [0.17, 0.78], 0.0097		1.26 [0.50, 3.19], 0.6306		0.62 [0.36, 1.08], 0.0917	
OR [95%-CI]; p-value	0.26 [0.09, 0.71], 0.0070		1.33 [0.42, 4.16], 0.6262		0.54 [0.26, 1.11], 0.0931	
RD [95%-CI]; p-value	-0.25 [-0.44, -0.06], 0.0097		0.04 [-0.13, 0.22], 0.6152		-0.11 [-0.24, 0.02], 0.1071	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.9665		0.0630		0.1769	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	11/29 (37.9)	14/59 (23.7)	6/31 (19.4)	26/118 (22.0)	17/60 (28.3)
RR [95%-CI]; p-value	0.54 [0.27, 1.07], 0.0753		1.23 [0.52, 2.87], 0.6392		0.78 [0.46, 1.32], 0.3492	
OR [95%-CI]; p-value	0.42 [0.16, 1.12], 0.0775		1.30 [0.44, 3.79], 0.6353		0.71 [0.35, 1.45], 0.3533	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.03], 0.0915		0.04 [-0.13, 0.22], 0.6270		-0.06 [-0.20, 0.07], 0.3652	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	9/33 (27.3)	6/60 (10.0)	8/29 (27.6)	14/116 (12.1)	17/62 (27.4)
RR [95%-CI]; p-value	0.52 [0.22, 1.23], 0.1358		0.36 [0.14, 0.95], 0.0385		0.44 [0.23, 0.83], 0.0115	
OR [95%-CI]; p-value	0.44 [0.15, 1.30], 0.1322		0.29 [0.09, 0.94], 0.0327		0.36 [0.16, 0.80], 0.0101	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1514		-0.18 [-0.36, 0.00], 0.0548		-0.15 [-0.28, -0.03], 0.0168	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8198		0.3494		0.6250	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	6/29 (20.7)	8/59 (13.6)	3/31 (9.7)	14/118 (11.9)	9/60 (15.0)
RR [95%-CI]; p-value	0.49 [0.17, 1.39], 0.1810		1.40 [0.40, 4.91], 0.5980		0.79 [0.36, 1.72], 0.5545	
OR [95%-CI]; p-value	0.43 [0.13, 1.49], 0.1765		1.46 [0.36, 5.97], 0.5932		0.76 [0.31, 1.88], 0.5555	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.06], 0.2153		0.04 [-0.10, 0.17], 0.5755		-0.03 [-0.14, 0.08], 0.5677	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	5/33 (15.2)	5/60 (8.3)	4/29 (13.8)	10/116 (8.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.59 [0.18, 1.88], 0.3726		0.60 [0.18, 2.08], 0.4249		0.59 [0.25, 1.38], 0.2274	
OR [95%-CI]; p-value	0.55 [0.15, 2.06], 0.3692		0.57 [0.14, 2.30], 0.4233		0.56 [0.21, 1.45], 0.2249	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.08], 0.3948		-0.05 [-0.20, 0.09], 0.4564		-0.06 [-0.16, 0.04], 0.2548	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.6761		0.2140		0.5381	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	7/59 (11.9)	5/29 (17.2)	9/59 (15.3)	2/31 (6.5)	16/118 (13.6)	7/60 (11.7)
RR [95%-CI]; p-value	0.69 [0.24, 1.98], 0.4887		2.36 [0.54, 10.28], 0.2510		1.16 [0.51, 2.67], 0.7232	
OR [95%-CI]; p-value	0.65 [0.19, 2.24], 0.4896		2.61 [0.53, 12.91], 0.2257		1.19 [0.46, 3.07], 0.7220	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5110		0.09 [-0.04, 0.21], 0.1712		0.02 [-0.08, 0.12], 0.7162	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	5/33 (15.2)	4/60 (6.7)	3/29 (10.3)	12/116 (10.3)	8/62 (12.9)
RR [95%-CI]; p-value	0.94 [0.34, 2.64], 0.9110		0.64 [0.15, 2.69], 0.5470		0.80 [0.35, 1.86], 0.6060	
OR [95%-CI]; p-value	0.93 [0.28, 3.13], 0.9111		0.62 [0.13, 2.97], 0.5457		0.78 [0.30, 2.02], 0.6066	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9116		-0.04 [-0.16, 0.09], 0.5719		-0.03 [-0.13, 0.07], 0.6167	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3473		0.0953		0.0572	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	4/59 (6.8)	3/29 (10.3)	6/59 (10.2)	0/31 (0.0)	10/118 (8.5)	3/60 (5.0)
RR [95%-CI]; p-value	0.66 [0.16, 2.74], 0.5623		6.41 [0.37, 111.02], 0.2019		1.69 [0.48, 5.93], 0.4089	
OR [95%-CI]; p-value	0.63 [0.13, 3.02], 0.5613		7.02 [0.38, 129.99], 0.1320		1.76 [0.47, 6.65], 0.3997	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.09], 0.5853		0.09 [-0.00, 0.17], 0.0577		0.03 [-0.04, 0.11], 0.3614	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	5/33 (15.2)	6/60 (10.0)	6/29 (20.7)	8/116 (6.9)	11/62 (17.7)
RR [95%-CI]; p-value	0.24 [0.05, 1.15], 0.0735		0.48 [0.17, 1.37], 0.1711		0.39 [0.16, 0.92], 0.0307	
OR [95%-CI]; p-value	0.21 [0.04, 1.14], 0.0500		0.43 [0.12, 1.46], 0.1664		0.34 [0.13, 0.91], 0.0256	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0847		-0.11 [-0.27, 0.06], 0.2064		-0.11 [-0.21, -0.00], 0.0443	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8323		0.3804		0.5422	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	4/29 (13.8)	2/59 (3.4)	1/31 (3.2)	8/118 (6.8)	5/60 (8.3)
RR [95%-CI]; p-value	0.74 [0.23, 2.41], 0.6140		1.05 [0.10, 11.14], 0.9672		0.81 [0.28, 2.38], 0.7063	
OR [95%-CI]; p-value	0.71 [0.18, 2.73], 0.6146		1.05 [0.09, 12.09], 0.9671		0.80 [0.25, 2.56], 0.7065	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6297		0.00 [-0.08, 0.08], 0.9669		-0.02 [-0.10, 0.07], 0.7149	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	4/33 (12.1)	4/60 (6.7)	6/29 (20.7)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.88 [0.27, 2.90], 0.8389		0.32 [0.10, 1.05], 0.0610		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.87 [0.23, 3.34], 0.8391		0.27 [0.07, 1.06], 0.0496		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.12], 0.8413		-0.14 [-0.30, 0.02], 0.0866		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.4.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4387		0.9692		0.3829	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	8/29 (27.6)	3/59 (5.1)	0/31 (0.0)	5/118 (4.2)	8/60 (13.3)
RR [95%-CI]; p-value	0.12 [0.03, 0.54], 0.0056		3.20 [0.17, 61.97], 0.4412		0.32 [0.11, 0.93], 0.0363	
OR [95%-CI]; p-value	0.09 [0.02, 0.47], 0.0008		3.32 [0.16, 68.46], 0.4111		0.29 [0.09, 0.92], 0.0275	
RD [95%-CI]; p-value	-0.24 [-0.41, -0.07], 0.0050		0.03 [-0.04, 0.11], 0.3346		-0.09 [-0.18, 0.00], 0.0562	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	4/33 (12.1)	3/60 (5.0)	0/29 (0.0)	5/116 (4.3)	4/62 (6.5)
RR [95%-CI]; p-value	0.29 [0.06, 1.52], 0.1447		2.95 [0.15, 57.00], 0.4740		0.67 [0.19, 2.40], 0.5363	
OR [95%-CI]; p-value	0.27 [0.05, 1.56], 0.1202		3.05 [0.15, 63.00], 0.4483		0.65 [0.17, 2.53], 0.5345	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1678		0.03 [-0.04, 0.11], 0.3695		-0.02 [-0.09, 0.05], 0.5570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_4_m_pt_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.4039		0.6794		0.2180	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	9/59 (15.3)	1/29 (3.4)	3/59 (5.1)	2/31 (6.5)	12/118 (10.2)	3/60 (5.0)
RR [95%-CI]; p-value	4.42 [0.59, 33.27], 0.1486		0.79 [0.14, 4.47], 0.7880		2.03 [0.60, 6.93], 0.2565	
OR [95%-CI]; p-value	5.04 [0.61, 41.87], 0.1009		0.78 [0.12, 4.91], 0.7879		2.15 [0.58, 7.94], 0.2405	
RD [95%-CI]; p-value	0.12 [0.00, 0.23], 0.0410		-0.01 [-0.12, 0.09], 0.7949		0.05 [-0.03, 0.13], 0.1914	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	1/33 (3.0)	3/60 (5.0)	3/29 (10.3)	5/116 (4.3)	4/62 (6.5)
RR [95%-CI]; p-value	1.18 [0.11, 12.50], 0.8915		0.48 [0.10, 2.25], 0.3541		0.67 [0.19, 2.40], 0.5363	
OR [95%-CI]; p-value	1.19 [0.10, 13.60], 0.8913		0.46 [0.09, 2.41], 0.3459		0.65 [0.17, 2.53], 0.5345	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8891		-0.05 [-0.18, 0.07], 0.3975		-0.02 [-0.09, 0.05], 0.5570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7374		NA		0.7769	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	0/29 (0.0)	0/59 (0.0)	0/31 (0.0)	0/118 (0.0)	0/60 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	0/60 (0.0)	0/29 (0.0)	1/116 (0.9)	0/62 (0.0)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		NA		1.08 [0.04, 31.67], 0.9654	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		NA		1.08 [0.04, 32.59], 0.9654	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		NA		0.00 [-0.03, 0.03], 0.9650	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2454		0.6794		0.1512	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	9/59 (15.3)	1/29 (3.4)	3/59 (5.1)	2/31 (6.5)	12/118 (10.2)	3/60 (5.0)
RR [95%-CI]; p-value	4.42 [0.59, 33.27], 0.1486		0.79 [0.14, 4.47], 0.7880		2.03 [0.60, 6.93], 0.2565	
OR [95%-CI]; p-value	5.04 [0.61, 41.87], 0.1009		0.78 [0.12, 4.91], 0.7879		2.15 [0.58, 7.94], 0.2405	
RD [95%-CI]; p-value	0.12 [0.00, 0.23], 0.0410		-0.01 [-0.12, 0.09], 0.7949		0.05 [-0.03, 0.13], 0.1914	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	1/33 (3.0)	3/60 (5.0)	3/29 (10.3)	4/116 (3.4)	4/62 (6.5)
RR [95%-CI]; p-value	0.59 [0.04, 9.11], 0.7050		0.48 [0.10, 2.25], 0.3541		0.53 [0.14, 2.06], 0.3635	
OR [95%-CI]; p-value	0.58 [0.04, 9.62], 0.7020		0.46 [0.09, 2.41], 0.3459		0.52 [0.12, 2.15], 0.3568	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.06], 0.7198		-0.05 [-0.18, 0.07], 0.3975		-0.03 [-0.10, 0.04], 0.3976	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8074		0.8137		0.9760	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	4/59 (6.8)	1/29 (3.4)	0/59 (0.0)	0/31 (0.0)	4/118 (3.4)	1/60 (1.7)
RR [95%-CI]; p-value	1.97 [0.23, 16.81], 0.5369		NA		2.03 [0.23, 17.80], 0.5212	
OR [95%-CI]; p-value	2.04 [0.22, 19.09], 0.5257		NA		2.07 [0.23, 18.94], 0.5107	
RD [95%-CI]; p-value	0.03 [-0.06, 0.13], 0.4795		NA		0.02 [-0.03, 0.06], 0.4628	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	1/60 (1.7)	0/29 (0.0)	2/116 (1.7)	0/62 (0.0)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		0.98 [0.03, 28.48], 0.9922		2.16 [0.10, 47.07], 0.6255	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		0.98 [0.03, 30.16], 0.9922		2.18 [0.10, 48.99], 0.6162	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		-0.00 [-0.06, 0.06], 0.9922		0.01 [-0.02, 0.04], 0.5760	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.5673		0.8069		0.5291	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	5/59 (8.5)	3/29 (10.3)	4/59 (6.8)	2/31 (6.5)	9/118 (7.6)	5/60 (8.3)
RR [95%-CI]; p-value	0.82 [0.21, 3.19], 0.7739		1.05 [0.20, 5.42], 0.9528		0.92 [0.32, 2.61], 0.8685	
OR [95%-CI]; p-value	0.80 [0.18, 3.62], 0.7742		1.05 [0.18, 6.10], 0.9527		0.91 [0.29, 2.84], 0.8686	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.11], 0.7807		0.00 [-0.10, 0.11], 0.9524		-0.01 [-0.09, 0.08], 0.8703	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	6/33 (18.2)	5/60 (8.3)	3/29 (10.3)	10/116 (8.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.49 [0.16, 1.48], 0.2076		0.81 [0.21, 3.14], 0.7555		0.59 [0.25, 1.38], 0.2274	
OR [95%-CI]; p-value	0.44 [0.12, 1.58], 0.2001		0.79 [0.17, 3.55], 0.7558		0.56 [0.21, 1.45], 0.2249	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.06], 0.2307		-0.02 [-0.15, 0.11], 0.7636		-0.06 [-0.16, 0.04], 0.2548	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.7374		0.7203		0.9843	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	0/29 (0.0)	1/59 (1.7)	0/31 (0.0)	1/118 (0.8)	0/60 (0.0)
RR [95%-CI]; p-value	NA		1.07 [0.04, 30.96], 0.9695		1.03 [0.03, 30.13], 0.9884	
OR [95%-CI]; p-value	NA		1.07 [0.03, 32.76], 0.9695		1.03 [0.03, 31.01], 0.9884	
RD [95%-CI]; p-value	NA		0.00 [-0.05, 0.06], 0.9692		0.00 [-0.03, 0.03], 0.9883	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	1/60 (1.7)	1/29 (3.4)	2/116 (1.7)	1/62 (1.6)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		0.48 [0.03, 7.46], 0.6025		1.07 [0.10, 11.56], 0.9562	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		0.47 [0.03, 7.87], 0.5951		1.07 [0.10, 12.04], 0.9562	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		-0.02 [-0.09, 0.06], 0.6365		0.00 [-0.04, 0.04], 0.9558	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.4255		0.9845		0.5514	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	5/59 (8.5)	3/29 (10.3)	3/59 (5.1)	2/31 (6.5)	8/118 (6.8)	5/60 (8.3)
RR [95%-CI]; p-value	0.82 [0.21, 3.19], 0.7739		0.79 [0.14, 4.47], 0.7880		0.81 [0.28, 2.38], 0.7063	
OR [95%-CI]; p-value	0.80 [0.18, 3.62], 0.7742		0.78 [0.12, 4.91], 0.7879		0.80 [0.25, 2.56], 0.7065	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.11], 0.7807		-0.01 [-0.12, 0.09], 0.7949		-0.02 [-0.10, 0.07], 0.7149	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	4/56 (7.1)	6/33 (18.2)	5/60 (8.3)	3/29 (10.3)	9/116 (7.8)	9/62 (14.5)
RR [95%-CI]; p-value	0.39 [0.12, 1.29], 0.1238		0.81 [0.21, 3.14], 0.7555		0.53 [0.22, 1.28], 0.1586	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1112		0.79 [0.17, 3.55], 0.7558		0.50 [0.19, 1.32], 0.1542	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1434		-0.02 [-0.15, 0.11], 0.7636		-0.07 [-0.17, 0.03], 0.1866	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9354		0.9622		0.8465	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	0/29 (0.0)	1/59 (1.7)	0/31 (0.0)	3/118 (2.5)	0/60 (0.0)
RR [95%-CI]; p-value	2.00 [0.09, 42.97], 0.6578		1.07 [0.04, 30.96], 0.9695		3.08 [0.16, 60.43], 0.4595	
OR [95%-CI]; p-value	2.04 [0.09, 46.60], 0.6501		1.07 [0.03, 32.76], 0.9695		3.13 [0.15, 63.52], 0.4338	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.6125		0.00 [-0.05, 0.06], 0.9692		0.02 [-0.02, 0.05], 0.3559	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	0/33 (0.0)	2/60 (3.3)	1/29 (3.4)	4/116 (3.4)	1/62 (1.6)
RR [95%-CI]; p-value	2.39 [0.11, 51.51], 0.5774		0.97 [0.09, 10.23], 0.9775		2.14 [0.24, 18.72], 0.4924	
OR [95%-CI]; p-value	2.44 [0.11, 55.86], 0.5635		0.97 [0.08, 11.10], 0.9775		2.18 [0.24, 19.93], 0.4801	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5219		-0.00 [-0.08, 0.08], 0.9777		0.02 [-0.03, 0.06], 0.4309	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.6.s2.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.4035		0.8851		0.3977	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	9/59 (15.3)	11/29 (37.9)	12/59 (20.3)	4/31 (12.9)	21/118 (17.8)	15/60 (25.0)
RR [95%-CI]; p-value	0.40 [0.19, 0.86], 0.0189		1.58 [0.55, 4.48], 0.3933		0.71 [0.40, 1.28], 0.2550	
OR [95%-CI]; p-value	0.29 [0.10, 0.83], 0.0170		1.72 [0.51, 5.88], 0.3806		0.65 [0.31, 1.38], 0.2580	
RD [95%-CI]; p-value	-0.23 [-0.43, -0.03], 0.0255		0.07 [-0.08, 0.23], 0.3516		-0.07 [-0.20, 0.06], 0.2756	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	7/56 (12.5)	6/33 (18.2)	11/60 (18.3)	3/29 (10.3)	18/116 (15.5)	9/62 (14.5)
RR [95%-CI]; p-value	0.69 [0.25, 1.87], 0.4636		1.77 [0.54, 5.87], 0.3488		1.07 [0.51, 2.24], 0.8595	
OR [95%-CI]; p-value	0.64 [0.20, 2.11], 0.4635		1.95 [0.50, 7.60], 0.3320		1.08 [0.45, 2.57], 0.8592	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4796		0.08 [-0.07, 0.23], 0.2897		0.01 [-0.10, 0.12], 0.8580	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_6_m_pt_adr_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.6162		0.6120		0.5834	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	40/58 (69.0)	22/30 (73.3)	35/60 (58.3)	13/24 (54.2)	75/118 (63.6)	35/54 (64.8)
RR [95%-CI]; p-value	0.94 [0.71, 1.24], 0.6632		1.08 [0.70, 1.65], 0.7329		0.98 [0.77, 1.25], 0.8727	
OR [95%-CI]; p-value	0.81 [0.30, 2.16], 0.6703		1.18 [0.46, 3.07], 0.7274		0.95 [0.48, 1.86], 0.8735	
RD [95%-CI]; p-value	-0.04 [-0.24, 0.15], 0.6655		0.04 [-0.19, 0.28], 0.7284		-0.01 [-0.17, 0.14], 0.8732	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	43/57 (75.4)	28/32 (87.5)	37/59 (62.7)	24/36 (66.7)	80/116 (69.0)	52/68 (76.5)
RR [95%-CI]; p-value	0.86 [0.71, 1.05], 0.1415		0.94 [0.69, 1.27], 0.6928		0.90 [0.75, 1.08], 0.2598	
OR [95%-CI]; p-value	0.44 [0.13, 1.47], 0.1740		0.84 [0.35, 2.01], 0.6965		0.68 [0.34, 1.36], 0.2751	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1397		-0.04 [-0.24, 0.16], 0.6945		-0.08 [-0.21, 0.06], 0.2628	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.9827		0.3106		0.3638	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	6/30 (20.0)	7/60 (11.7)	2/24 (8.3)	15/118 (12.7)	8/54 (14.8)
RR [95%-CI]; p-value	0.69 [0.26, 1.81], 0.4492		1.40 [0.31, 6.26], 0.6599		0.86 [0.39, 1.90], 0.7060	
OR [95%-CI]; p-value	0.64 [0.20, 2.05], 0.4505		1.45 [0.28, 7.55], 0.6554		0.84 [0.33, 2.11], 0.7069	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4701		0.03 [-0.10, 0.17], 0.6340		-0.02 [-0.13, 0.09], 0.7134	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	4/32 (12.5)	6/59 (10.2)	0/36 (0.0)	11/116 (9.5)	4/68 (5.9)
RR [95%-CI]; p-value	0.70 [0.20, 2.43], 0.5761		7.42 [0.43, 129.02], 0.1688		1.61 [0.53, 4.86], 0.3968	
OR [95%-CI]; p-value	0.67 [0.17, 2.71], 0.5756		8.15 [0.44, 150.51], 0.0971		1.68 [0.51, 5.49], 0.3890	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.10], 0.5914		0.09 [0.00, 0.17], 0.0445		0.04 [-0.04, 0.11], 0.3611	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.3457		0.6541		0.6014	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	6/58 (10.3)	3/30 (10.0)	0/60 (0.0)	1/24 (4.2)	6/118 (5.1)	4/54 (7.4)
RR [95%-CI]; p-value	1.03 [0.28, 3.85], 0.9597		0.20 [0.01, 5.72], 0.3456		0.69 [0.20, 2.33], 0.5467	
OR [95%-CI]; p-value	1.04 [0.24, 4.48], 0.9596		0.19 [0.01, 5.91], 0.2944		0.67 [0.18, 2.48], 0.5458	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9594		-0.03 [-0.12, 0.05], 0.4310		-0.02 [-0.10, 0.06], 0.5708	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	1/32 (3.1)	3/59 (5.1)	4/36 (11.1)	9/116 (7.8)	5/68 (7.4)
RR [95%-CI]; p-value	3.37 [0.42, 26.75], 0.2507		0.46 [0.11, 1.93], 0.2868		1.06 [0.37, 3.02], 0.9203	
OR [95%-CI]; p-value	3.65 [0.42, 31.74], 0.2132		0.43 [0.09, 2.04], 0.2754		1.06 [0.34, 3.30], 0.9202	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1465		-0.06 [-0.18, 0.06], 0.3126		0.00 [-0.07, 0.08], 0.9197	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.6380		0.3837		0.3868	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	3/30 (10.0)	5/60 (8.3)	1/24 (4.2)	13/118 (11.0)	4/54 (7.4)
RR [95%-CI]; p-value	1.38 [0.39, 4.82], 0.6145		2.00 [0.25, 16.24], 0.5165		1.49 [0.51, 4.35], 0.4686	
OR [95%-CI]; p-value	1.44 [0.35, 5.88], 0.6101		2.09 [0.23, 18.90], 0.5029		1.55 [0.48, 4.99], 0.4616	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5935		0.04 [-0.06, 0.15], 0.4420		0.04 [-0.05, 0.13], 0.4310	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	12/57 (21.1)	7/32 (21.9)	7/59 (11.9)	6/36 (16.7)	19/116 (16.4)	13/68 (19.1)
RR [95%-CI]; p-value	0.96 [0.42, 2.20], 0.9275		0.71 [0.26, 1.95], 0.5090		0.86 [0.45, 1.62], 0.6353	
OR [95%-CI]; p-value	0.95 [0.33, 2.73], 0.9276		0.67 [0.21, 2.19], 0.5088		0.83 [0.38, 1.81], 0.6362	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9279		-0.05 [-0.20, 0.10], 0.5222		-0.03 [-0.14, 0.09], 0.6413	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9425		0.9963		0.8261	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	1/30 (3.3)	3/60 (5.0)	0/24 (0.0)	6/118 (5.1)	1/54 (1.9)
RR [95%-CI]; p-value	1.55 [0.17, 14.28], 0.6981		2.45 [0.13, 47.13], 0.5525		2.75 [0.34, 22.25], 0.3441	
OR [95%-CI]; p-value	1.58 [0.16, 15.90], 0.6946		2.53 [0.12, 52.37], 0.5356		2.84 [0.33, 24.18], 0.3193	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6747		0.03 [-0.05, 0.11], 0.4605		0.03 [-0.02, 0.09], 0.2364	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	2/32 (6.3)	2/59 (3.4)	0/36 (0.0)	7/116 (6.0)	2/68 (2.9)
RR [95%-CI]; p-value	1.40 [0.29, 6.83], 0.6744		2.47 [0.11, 53.38], 0.5631		2.05 [0.44, 9.60], 0.3612	
OR [95%-CI]; p-value	1.44 [0.26, 7.90], 0.6715		2.53 [0.11, 57.61], 0.5480		2.12 [0.43, 10.51], 0.3477	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6575		0.02 [-0.04, 0.08], 0.5066		0.03 [-0.03, 0.09], 0.3048	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.5390		NA		0.4999	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	0/58 (0.0)	1/30 (3.3)	0/60 (0.0)	0/24 (0.0)	0/118 (0.0)	1/54 (1.9)
RR [95%-CI]; p-value	0.26 [0.01, 7.43], 0.4281		NA		0.23 [0.01, 6.69], 0.3910	
OR [95%-CI]; p-value	0.25 [0.01, 7.67], 0.3925		NA		0.22 [0.01, 6.80], 0.3482	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.04], 0.4777		NA		-0.01 [-0.05, 0.02], 0.4585	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	1/116 (0.9)	0/68 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.07], 0.9391		NA		1.18 [0.04, 34.74], 0.9232	
OR [95%-CI]; p-value	1.14 [0.04, 35.02], 0.9390		NA		1.18 [0.04, 35.72], 0.9231	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9379		NA		0.00 [-0.02, 0.03], 0.9214	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7635		NA		0.7191	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	0/58 (0.0)	1/30 (3.3)	0/60 (0.0)	0/24 (0.0)	0/118 (0.0)	1/54 (1.9)
RR [95%-CI]; p-value	0.26 [0.01, 7.43], 0.4281		NA		0.23 [0.01, 6.69], 0.3910	
OR [95%-CI]; p-value	0.25 [0.01, 7.67], 0.3925		NA		0.22 [0.01, 6.80], 0.3482	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.04], 0.4777		NA		-0.01 [-0.05, 0.02], 0.4585	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	0/57 (0.0)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	0/116 (0.0)	0/68 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.6171		0.1494		0.2338	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	35/58 (60.3)	21/30 (70.0)	32/60 (53.3)	9/24 (37.5)	67/118 (56.8)	30/54 (55.6)
RR [95%-CI]; p-value	0.86 [0.63, 1.18], 0.3538		1.42 [0.81, 2.51], 0.2243		1.02 [0.77, 1.36], 0.8812	
OR [95%-CI]; p-value	0.65 [0.25, 1.67], 0.3721		1.90 [0.72, 5.02], 0.1897		1.05 [0.55, 2.01], 0.8806	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3600		0.16 [-0.07, 0.39], 0.1795		0.01 [-0.15, 0.17], 0.8807	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	33/57 (57.9)	24/32 (75.0)	28/59 (47.5)	20/36 (55.6)	61/116 (52.6)	44/68 (64.7)
RR [95%-CI]; p-value	0.77 [0.57, 1.04], 0.0891		0.85 [0.57, 1.27], 0.4365		0.81 [0.64, 1.04], 0.0989	
OR [95%-CI]; p-value	0.46 [0.18, 1.19], 0.1066		0.72 [0.31, 1.66], 0.4438		0.60 [0.33, 1.12], 0.1089	
RD [95%-CI]; p-value	-0.17 [-0.37, 0.03], 0.0893		-0.08 [-0.29, 0.13], 0.4418		-0.12 [-0.27, 0.02], 0.1025	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.5192		0.7978		0.4793	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	15/58 (25.9)	11/30 (36.7)	16/60 (26.7)	6/24 (25.0)	31/118 (26.3)	17/54 (31.5)
RR [95%-CI]; p-value	0.71 [0.37, 1.34], 0.2859		1.07 [0.47, 2.40], 0.8759		0.83 [0.51, 1.37], 0.4748	
OR [95%-CI]; p-value	0.60 [0.23, 1.55], 0.2923		1.09 [0.37, 3.23], 0.8753		0.78 [0.38, 1.57], 0.4796	
RD [95%-CI]; p-value	-0.11 [-0.31, 0.10], 0.3039		0.02 [-0.19, 0.22], 0.8741		-0.05 [-0.20, 0.10], 0.4877	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	23/57 (40.4)	14/32 (43.8)	20/59 (33.9)	10/36 (27.8)	43/116 (37.1)	24/68 (35.3)
RR [95%-CI]; p-value	0.92 [0.56, 1.53], 0.7531		1.22 [0.65, 2.30], 0.5394		1.05 [0.70, 1.57], 0.8099	
OR [95%-CI]; p-value	0.87 [0.36, 2.09], 0.7549		1.33 [0.54, 3.30], 0.5335		1.08 [0.58, 2.02], 0.8092	
RD [95%-CI]; p-value	-0.03 [-0.25, 0.18], 0.7555		0.06 [-0.13, 0.25], 0.5272		0.02 [-0.13, 0.16], 0.8086	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.3457		0.6541		0.6014	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	6/58 (10.3)	3/30 (10.0)	0/60 (0.0)	1/24 (4.2)	6/118 (5.1)	4/54 (7.4)
RR [95%-CI]; p-value	1.03 [0.28, 3.85], 0.9597		0.20 [0.01, 5.72], 0.3456		0.69 [0.20, 2.33], 0.5467	
OR [95%-CI]; p-value	1.04 [0.24, 4.48], 0.9596		0.19 [0.01, 5.91], 0.2944		0.67 [0.18, 2.48], 0.5458	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9594		-0.03 [-0.12, 0.05], 0.4310		-0.02 [-0.10, 0.06], 0.5708	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	1/32 (3.1)	3/59 (5.1)	4/36 (11.1)	9/116 (7.8)	5/68 (7.4)
RR [95%-CI]; p-value	3.37 [0.42, 26.75], 0.2507		0.46 [0.11, 1.93], 0.2868		1.06 [0.37, 3.02], 0.9203	
OR [95%-CI]; p-value	3.65 [0.42, 31.74], 0.2132		0.43 [0.09, 2.04], 0.2754		1.06 [0.34, 3.30], 0.9202	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1465		-0.06 [-0.18, 0.06], 0.3126		0.00 [-0.07, 0.08], 0.9197	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.9173		0.6521		0.9055	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	3/30 (10.0)	3/60 (5.0)	1/24 (4.2)	6/118 (5.1)	4/54 (7.4)
RR [95%-CI]; p-value	0.52 [0.11, 2.41], 0.4010		1.20 [0.13, 10.97], 0.8717		0.69 [0.20, 2.33], 0.5467	
OR [95%-CI]; p-value	0.49 [0.09, 2.60], 0.3944		1.21 [0.12, 12.25], 0.8713		0.67 [0.18, 2.48], 0.5458	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.07], 0.4363		0.01 [-0.09, 0.11], 0.8664		-0.02 [-0.10, 0.06], 0.5708	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	6/32 (18.8)	4/59 (6.8)	1/36 (2.8)	9/116 (7.8)	7/68 (10.3)
RR [95%-CI]; p-value	0.47 [0.15, 1.41], 0.1779		2.44 [0.28, 20.99], 0.4164		0.75 [0.29, 1.93], 0.5560	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1699		2.55 [0.27, 23.72], 0.3968		0.73 [0.26, 2.07], 0.5557	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.2038		0.04 [-0.04, 0.12], 0.3484		-0.03 [-0.11, 0.06], 0.5683	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4484		0.3292		0.4487	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	8/30 (26.7)	11/60 (18.3)	1/24 (4.2)	23/118 (19.5)	9/54 (16.7)
RR [95%-CI]; p-value	0.78 [0.36, 1.69], 0.5229		4.40 [0.60, 32.24], 0.1448		1.17 [0.58, 2.36], 0.6612	
OR [95%-CI]; p-value	0.72 [0.26, 2.01], 0.5259		5.16 [0.63, 42.43], 0.0937		1.21 [0.52, 2.83], 0.6586	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5364		0.14 [0.02, 0.27], 0.0280		0.03 [-0.09, 0.15], 0.6511	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	9/57 (15.8)	10/32 (31.3)	12/59 (20.3)	5/36 (13.9)	21/116 (18.1)	15/68 (22.1)
RR [95%-CI]; p-value	0.51 [0.23, 1.11], 0.0902		1.46 [0.56, 3.81], 0.4349		0.82 [0.45, 1.48], 0.5123	
OR [95%-CI]; p-value	0.41 [0.15, 1.16], 0.0876		1.58 [0.51, 4.94], 0.4262		0.78 [0.37, 1.64], 0.5139	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.03], 0.1041		0.06 [-0.09, 0.22], 0.4077		-0.04 [-0.16, 0.08], 0.5215	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.9013		0.9216		0.6662	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	7/30 (23.3)	5/60 (8.3)	2/24 (8.3)	12/118 (10.2)	9/54 (16.7)
RR [95%-CI]; p-value	0.52 [0.20, 1.34], 0.1740		1.00 [0.21, 4.81], 1.0000		0.61 [0.27, 1.36], 0.2273	
OR [95%-CI]; p-value	0.45 [0.14, 1.44], 0.1709		1.00 [0.18, 5.54], 1.0000		0.57 [0.22, 1.44], 0.2271	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.06], 0.2019		0.00 [-0.13, 0.13], 1.0000		-0.06 [-0.18, 0.05], 0.2614	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	8/32 (25.0)	9/59 (15.3)	5/36 (13.9)	17/116 (14.7)	13/68 (19.1)
RR [95%-CI]; p-value	0.56 [0.23, 1.35], 0.1981		1.10 [0.40, 3.02], 0.8558		0.77 [0.40, 1.48], 0.4279	
OR [95%-CI]; p-value	0.49 [0.16, 1.46], 0.1961		1.12 [0.34, 3.64], 0.8555		0.73 [0.33, 1.61], 0.4290	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2195		0.01 [-0.13, 0.16], 0.8541		-0.04 [-0.16, 0.07], 0.4409	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.5158		0.8373		0.7787	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	16/58 (27.6)	7/30 (23.3)	12/60 (20.0)	5/24 (20.8)	28/118 (23.7)	12/54 (22.2)
RR [95%-CI]; p-value	1.18 [0.55, 2.56], 0.6704		0.96 [0.38, 2.43], 0.9314		1.07 [0.59, 1.94], 0.8288	
OR [95%-CI]; p-value	1.25 [0.45, 3.48], 0.6669		0.95 [0.29, 3.06], 0.9316		1.09 [0.50, 2.35], 0.8282	
RD [95%-CI]; p-value	0.04 [-0.15, 0.23], 0.6610		-0.01 [-0.20, 0.18], 0.9320		0.02 [-0.12, 0.15], 0.8267	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	15/57 (26.3)	10/32 (31.3)	16/59 (27.1)	9/36 (25.0)	31/116 (26.7)	19/68 (27.9)
RR [95%-CI]; p-value	0.84 [0.43, 1.65], 0.6167		1.08 [0.54, 2.19], 0.8207		0.96 [0.59, 1.56], 0.8576	
OR [95%-CI]; p-value	0.79 [0.30, 2.04], 0.6192		1.12 [0.43, 2.88], 0.8200		0.94 [0.48, 1.84], 0.8578	
RD [95%-CI]; p-value	-0.05 [-0.25, 0.15], 0.6237		0.02 [-0.16, 0.20], 0.8189		-0.01 [-0.15, 0.12], 0.8583	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2503		0.6085		0.2470	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	9/58 (15.5)	4/30 (13.3)	7/60 (11.7)	2/24 (8.3)	16/118 (13.6)	6/54 (11.1)
RR [95%-CI]; p-value	1.16 [0.39, 3.47], 0.7855		1.40 [0.31, 6.26], 0.6599		1.22 [0.51, 2.95], 0.6579	
OR [95%-CI]; p-value	1.19 [0.34, 4.25], 0.7843		1.45 [0.28, 7.55], 0.6554		1.25 [0.46, 3.41], 0.6555	
RD [95%-CI]; p-value	0.02 [-0.13, 0.18], 0.7800		0.03 [-0.10, 0.17], 0.6340		0.02 [-0.08, 0.13], 0.6449	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	6/32 (18.8)	4/59 (6.8)	3/36 (8.3)	9/116 (7.8)	9/68 (13.2)
RR [95%-CI]; p-value	0.47 [0.15, 1.41], 0.1779		0.81 [0.19, 3.43], 0.7786		0.59 [0.24, 1.40], 0.2311	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1699		0.80 [0.17, 3.80], 0.7786		0.55 [0.21, 1.46], 0.2274	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.2038		-0.02 [-0.13, 0.10], 0.7834		-0.05 [-0.15, 0.04], 0.2541	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5948		0.7957		0.7736	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	13/58 (22.4)	9/30 (30.0)	8/60 (13.3)	3/24 (12.5)	21/118 (17.8)	12/54 (22.2)
RR [95%-CI]; p-value	0.75 [0.36, 1.55], 0.4317		1.07 [0.31, 3.68], 0.9187		0.80 [0.43, 1.51], 0.4910	
OR [95%-CI]; p-value	0.67 [0.25, 1.82], 0.4360		1.08 [0.26, 4.46], 0.9185		0.76 [0.34, 1.68], 0.4939	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.12], 0.4480		0.01 [-0.15, 0.17], 0.9176		-0.04 [-0.17, 0.09], 0.5066	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	10/57 (17.5)	10/32 (31.3)	13/59 (22.0)	9/36 (25.0)	23/116 (19.8)	19/68 (27.9)
RR [95%-CI]; p-value	0.56 [0.26, 1.20], 0.1376		0.88 [0.42, 1.85], 0.7387		0.71 [0.42, 1.20], 0.2036	
OR [95%-CI]; p-value	0.47 [0.17, 1.29], 0.1371		0.85 [0.32, 2.24], 0.7395		0.64 [0.32, 1.28], 0.2056	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1542		-0.03 [-0.21, 0.15], 0.7420		-0.08 [-0.21, 0.05], 0.2176	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3472		0.0175		0.0219	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	9/30 (30.0)	13/60 (21.7)	2/24 (8.3)	25/118 (21.2)	11/54 (20.4)
RR [95%-CI]; p-value	0.69 [0.33, 1.45], 0.3273		2.60 [0.63, 10.66], 0.1846		1.04 [0.55, 1.96], 0.9030	
OR [95%-CI]; p-value	0.61 [0.22, 1.67], 0.3314		3.04 [0.63, 14.66], 0.1495		1.05 [0.47, 2.33], 0.9028	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.10], 0.3477		0.13 [-0.02, 0.29], 0.0855		0.01 [-0.12, 0.14], 0.9023	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	11/32 (34.4)	7/59 (11.9)	12/36 (33.3)	15/116 (12.9)	23/68 (33.8)
RR [95%-CI]; p-value	0.41 [0.18, 0.91], 0.0284		0.36 [0.15, 0.82], 0.0153		0.38 [0.21, 0.68], 0.0011	
OR [95%-CI]; p-value	0.31 [0.11, 0.89], 0.0246		0.27 [0.09, 0.77], 0.0112		0.29 [0.14, 0.61], 0.0007	
RD [95%-CI]; p-value	-0.20 [-0.39, -0.02], 0.0336		-0.21 [-0.39, -0.04], 0.0160		-0.21 [-0.34, -0.08], 0.0014	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.9180		0.1935		0.4617	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	5/58 (8.6)	5/30 (16.7)	7/60 (11.7)	1/24 (4.2)	12/118 (10.2)	6/54 (11.1)
RR [95%-CI]; p-value	0.52 [0.16, 1.65], 0.2647		2.80 [0.36, 21.56], 0.3228		0.92 [0.36, 2.31], 0.8513	
OR [95%-CI]; p-value	0.47 [0.13, 1.78], 0.2596		3.04 [0.35, 26.12], 0.2901		0.91 [0.32, 2.56], 0.8515	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2984		0.08 [-0.04, 0.19], 0.1971		-0.01 [-0.11, 0.09], 0.8536	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	6/32 (18.8)	6/59 (10.2)	6/36 (16.7)	12/116 (10.3)	12/68 (17.6)
RR [95%-CI]; p-value	0.56 [0.20, 1.60], 0.2791		0.61 [0.21, 1.75], 0.3578		0.59 [0.28, 1.23], 0.1583	
OR [95%-CI]; p-value	0.51 [0.15, 1.74], 0.2757		0.57 [0.17, 1.91], 0.3551		0.54 [0.23, 1.28], 0.1557	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.3045		-0.06 [-0.21, 0.08], 0.3769		-0.07 [-0.18, 0.03], 0.1778	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.5887		0.7473		0.8294	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	4/30 (13.3)	2/60 (3.3)	0/24 (0.0)	5/118 (4.2)	4/54 (7.4)
RR [95%-CI]; p-value	0.39 [0.09, 1.62], 0.1945		1.63 [0.08, 34.94], 0.7536		0.57 [0.16, 2.05], 0.3904	
OR [95%-CI]; p-value	0.35 [0.07, 1.70], 0.1799		1.66 [0.07, 38.06], 0.7504		0.55 [0.14, 2.15], 0.3862	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2338		0.01 [-0.06, 0.09], 0.7253		-0.03 [-0.11, 0.05], 0.4301	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	3/32 (9.4)	3/59 (5.1)	2/36 (5.6)	4/116 (3.4)	5/68 (7.4)
RR [95%-CI]; p-value	0.19 [0.02, 1.73], 0.1392		0.92 [0.16, 5.22], 0.9206		0.47 [0.13, 1.69], 0.2464	
OR [95%-CI]; p-value	0.17 [0.02, 1.73], 0.0959		0.91 [0.14, 5.73], 0.9206		0.45 [0.12, 1.74], 0.2359	
RD [95%-CI]; p-value	-0.08 [-0.18, 0.03], 0.1611		-0.00 [-0.10, 0.09], 0.9214		-0.04 [-0.11, 0.03], 0.2768	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4170		0.8929		0.5255	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	6/30 (20.0)	7/60 (11.7)	2/24 (8.3)	14/118 (11.9)	8/54 (14.8)
RR [95%-CI]; p-value	0.60 [0.22, 1.64], 0.3209		1.40 [0.31, 6.26], 0.6599		0.80 [0.36, 1.79], 0.5895	
OR [95%-CI]; p-value	0.55 [0.17, 1.81], 0.3203		1.45 [0.28, 7.55], 0.6554		0.77 [0.30, 1.97], 0.5908	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3487		0.03 [-0.10, 0.17], 0.6340		-0.03 [-0.14, 0.08], 0.6033	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	4/32 (12.5)	6/59 (10.2)	3/36 (8.3)	14/116 (12.1)	7/68 (10.3)
RR [95%-CI]; p-value	1.12 [0.37, 3.44], 0.8393		1.22 [0.33, 4.58], 0.7679		1.17 [0.50, 2.76], 0.7159	
OR [95%-CI]; p-value	1.14 [0.32, 4.14], 0.8388		1.25 [0.29, 5.32], 0.7669		1.20 [0.46, 3.13], 0.7148	
RD [95%-CI]; p-value	0.02 [-0.13, 0.16], 0.8365		0.02 [-0.10, 0.14], 0.7618		0.02 [-0.08, 0.11], 0.7097	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0990		0.3403		0.0226	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	0/30 (0.0)	8/60 (13.3)	2/24 (8.3)	11/118 (9.3)	2/54 (3.7)
RR [95%-CI]; p-value	3.16 [0.16, 60.99], 0.4470		1.60 [0.37, 7.00], 0.5324		2.52 [0.58, 10.97], 0.2190	
OR [95%-CI]; p-value	3.27 [0.16, 67.52], 0.4177		1.69 [0.33, 8.62], 0.5227		2.67 [0.57, 12.50], 0.1958	
RD [95%-CI]; p-value	0.04 [-0.04, 0.11], 0.3406		0.05 [-0.09, 0.19], 0.4842		0.06 [-0.02, 0.13], 0.1300	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	8/32 (25.0)	4/59 (6.8)	4/36 (11.1)	7/116 (6.0)	12/68 (17.6)
RR [95%-CI]; p-value	0.21 [0.06, 0.74], 0.0149		0.61 [0.16, 2.29], 0.4641		0.34 [0.14, 0.83], 0.0172	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0066		0.58 [0.14, 2.49], 0.4608		0.30 [0.11, 0.80], 0.0125	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0162		-0.04 [-0.16, 0.08], 0.4831		-0.12 [-0.22, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7689		0.6603		0.9926	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	3/30 (10.0)	3/60 (5.0)	2/24 (8.3)	7/118 (5.9)	5/54 (9.3)
RR [95%-CI]; p-value	0.69 [0.16, 2.88], 0.6107		0.60 [0.11, 3.37], 0.5617		0.64 [0.21, 1.93], 0.4282	
OR [95%-CI]; p-value	0.67 [0.14, 3.19], 0.6101		0.58 [0.09, 3.70], 0.5597		0.62 [0.19, 2.04], 0.4267	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6282		-0.03 [-0.16, 0.09], 0.5970		-0.03 [-0.12, 0.06], 0.4601	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	5/32 (15.6)	3/59 (5.1)	5/36 (13.9)	11/116 (9.5)	10/68 (14.7)
RR [95%-CI]; p-value	0.90 [0.32, 2.52], 0.8382		0.37 [0.09, 1.44], 0.1506		0.64 [0.29, 1.44], 0.2838	
OR [95%-CI]; p-value	0.88 [0.26, 2.96], 0.8385		0.33 [0.07, 1.48], 0.1339		0.61 [0.24, 1.52], 0.2821	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8404		-0.09 [-0.21, 0.04], 0.1712		-0.05 [-0.15, 0.05], 0.3042	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.3.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3457		0.8458		0.4349	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	6/30 (20.0)	3/60 (5.0)	0/24 (0.0)	4/118 (3.4)	6/54 (11.1)
RR [95%-CI]; p-value	0.09 [0.01, 0.68], 0.0203		2.45 [0.13, 47.13], 0.5525		0.31 [0.09, 1.04], 0.0572	
OR [95%-CI]; p-value	0.07 [0.01, 0.61], 0.0027		2.53 [0.12, 52.37], 0.5356		0.28 [0.08, 1.04], 0.0446	
RD [95%-CI]; p-value	-0.18 [-0.33, -0.04], 0.0148		0.03 [-0.05, 0.11], 0.4605		-0.08 [-0.17, 0.01], 0.0925	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	6/32 (18.8)	3/59 (5.1)	0/36 (0.0)	6/116 (5.2)	6/68 (8.8)
RR [95%-CI]; p-value	0.28 [0.08, 1.05], 0.0586		3.71 [0.19, 72.01], 0.3860		0.59 [0.20, 1.75], 0.3374	
OR [95%-CI]; p-value	0.24 [0.06, 1.04], 0.0429		3.86 [0.19, 79.28], 0.3478		0.56 [0.17, 1.82], 0.3329	
RD [95%-CI]; p-value	-0.13 [-0.28, 0.01], 0.0724		0.04 [-0.03, 0.10], 0.2812		-0.04 [-0.12, 0.04], 0.3622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_3_m_pt_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.3.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.1244		0.9690		0.3797	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	3/30 (10.0)	2/60 (3.3)	0/24 (0.0)	6/118 (5.1)	3/54 (5.6)
RR [95%-CI]; p-value	0.69 [0.16, 2.88], 0.6107		1.63 [0.08, 34.94], 0.7536		0.92 [0.24, 3.52], 0.8975	
OR [95%-CI]; p-value	0.67 [0.14, 3.19], 0.6101		1.66 [0.07, 38.06], 0.7504		0.91 [0.22, 3.79], 0.8976	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6282		0.01 [-0.06, 0.09], 0.7253		-0.00 [-0.08, 0.07], 0.8992	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	0/57 (0.0)	5/32 (15.6)	5/59 (8.5)	2/36 (5.6)	5/116 (4.3)	7/68 (10.3)
RR [95%-CI]; p-value	0.06 [0.00, 0.99], 0.0489		1.53 [0.31, 7.45], 0.6019		0.42 [0.14, 1.27], 0.1235	
OR [95%-CI]; p-value	0.05 [0.00, 0.90], 0.0053		1.57 [0.29, 8.57], 0.5973		0.39 [0.12, 1.29], 0.1126	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.02], 0.0239		0.03 [-0.07, 0.13], 0.5793		-0.06 [-0.14, 0.02], 0.1483	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_3_m_pt_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.3.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.9526		0.4123		0.6475	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	2/58 (3.4)	1/30 (3.3)	2/60 (3.3)	1/24 (4.2)	4/118 (3.4)	2/54 (3.7)
RR [95%-CI]; p-value	1.03 [0.10, 10.95], 0.9775		0.80 [0.08, 8.42], 0.8526		0.92 [0.17, 4.85], 0.9171	
OR [95%-CI]; p-value	1.04 [0.09, 11.91], 0.9775		0.79 [0.07, 9.18], 0.8525		0.91 [0.16, 5.14], 0.9171	
RD [95%-CI]; p-value	0.00 [-0.08, 0.08], 0.9774		-0.01 [-0.10, 0.08], 0.8590		-0.00 [-0.06, 0.06], 0.9184	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	3/32 (9.4)	2/59 (3.4)	5/36 (13.9)	8/116 (6.9)	8/68 (11.8)
RR [95%-CI]; p-value	1.12 [0.30, 4.19], 0.8631		0.24 [0.05, 1.19], 0.0815		0.59 [0.23, 1.49], 0.2620	
OR [95%-CI]; p-value	1.14 [0.26, 4.89], 0.8627		0.22 [0.04, 1.19], 0.0574		0.56 [0.20, 1.56], 0.2580	
RD [95%-CI]; p-value	0.01 [-0.12, 0.14], 0.8607		-0.10 [-0.23, 0.02], 0.0918		-0.05 [-0.14, 0.04], 0.2858	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_3_m_pt_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.8.1.1.s3.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.7768		0.4992		0.3034	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	0/30 (0.0)	1/60 (1.7)	0/24 (0.0)	2/118 (1.7)	0/54 (0.0)
RR [95%-CI]; p-value	1.05 [0.04, 30.47], 0.9766		0.82 [0.03, 23.56], 0.9060		1.85 [0.08, 40.29], 0.6963	
OR [95%-CI]; p-value	1.05 [0.03, 32.29], 0.9766		0.81 [0.03, 25.06], 0.9059		1.86 [0.08, 41.99], 0.6912	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9764		-0.00 [-0.07, 0.06], 0.9097		0.01 [-0.03, 0.04], 0.6578	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	1/32 (3.1)	1/59 (1.7)	3/36 (8.3)	2/116 (1.7)	4/68 (5.9)
RR [95%-CI]; p-value	0.56 [0.04, 8.68], 0.6794		0.20 [0.02, 1.88], 0.1606		0.29 [0.06, 1.56], 0.1500	
OR [95%-CI]; p-value	0.55 [0.03, 9.16], 0.6755		0.19 [0.02, 1.90], 0.1181		0.28 [0.05, 1.58], 0.1253	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.06], 0.6981		-0.07 [-0.16, 0.03], 0.1758		-0.04 [-0.10, 0.02], 0.1796	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_8_1_1_m_soc_sae5pct_wt_pp.sas using SAS 9.4

Table 12.4.8.1.2.s3.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_8_1_2_m_pt_sae5pct_wt_pp.sas using SAS 9.4

Table 12.4.5.1.1.s3.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_5_1_1_m_soc_aeg35pct_wt_pp.sas using SAS 9.4

Table 12.4.5.1.2.s3.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_5_1_2_m_pt_aeg35pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4484		0.3292		0.4487	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	8/30 (26.7)	11/60 (18.3)	1/24 (4.2)	23/118 (19.5)	9/54 (16.7)
RR [95%-CI]; p-value	0.78 [0.36, 1.69], 0.5229		4.40 [0.60, 32.24], 0.1448		1.17 [0.58, 2.36], 0.6612	
OR [95%-CI]; p-value	0.72 [0.26, 2.01], 0.5259		5.16 [0.63, 42.43], 0.0937		1.21 [0.52, 2.83], 0.6586	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5364		0.14 [0.02, 0.27], 0.0280		0.03 [-0.09, 0.15], 0.6511	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	9/57 (15.8)	10/32 (31.3)	12/59 (20.3)	5/36 (13.9)	21/116 (18.1)	15/68 (22.1)
RR [95%-CI]; p-value	0.51 [0.23, 1.11], 0.0902		1.46 [0.56, 3.81], 0.4349		0.82 [0.45, 1.48], 0.5123	
OR [95%-CI]; p-value	0.41 [0.15, 1.16], 0.0876		1.58 [0.51, 4.94], 0.4262		0.78 [0.37, 1.64], 0.5139	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.03], 0.1041		0.06 [-0.09, 0.22], 0.4077		-0.04 [-0.16, 0.08], 0.5215	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.9013		0.9216		0.6662	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	7/30 (23.3)	5/60 (8.3)	2/24 (8.3)	12/118 (10.2)	9/54 (16.7)
RR [95%-CI]; p-value	0.52 [0.20, 1.34], 0.1740		1.00 [0.21, 4.81], 1.0000		0.61 [0.27, 1.36], 0.2273	
OR [95%-CI]; p-value	0.45 [0.14, 1.44], 0.1709		1.00 [0.18, 5.54], 1.0000		0.57 [0.22, 1.44], 0.2271	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.06], 0.2019		0.00 [-0.13, 0.13], 1.0000		-0.06 [-0.18, 0.05], 0.2614	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	8/32 (25.0)	9/59 (15.3)	5/36 (13.9)	17/116 (14.7)	13/68 (19.1)
RR [95%-CI]; p-value	0.56 [0.23, 1.35], 0.1981		1.10 [0.40, 3.02], 0.8558		0.77 [0.40, 1.48], 0.4279	
OR [95%-CI]; p-value	0.49 [0.16, 1.46], 0.1961		1.12 [0.34, 3.64], 0.8555		0.73 [0.33, 1.61], 0.4290	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2195		0.01 [-0.13, 0.16], 0.8541		-0.04 [-0.16, 0.07], 0.4409	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.5158		0.8373		0.7787	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	16/58 (27.6)	7/30 (23.3)	12/60 (20.0)	5/24 (20.8)	28/118 (23.7)	12/54 (22.2)
RR [95%-CI]; p-value	1.18 [0.55, 2.56], 0.6704		0.96 [0.38, 2.43], 0.9314		1.07 [0.59, 1.94], 0.8288	
OR [95%-CI]; p-value	1.25 [0.45, 3.48], 0.6669		0.95 [0.29, 3.06], 0.9316		1.09 [0.50, 2.35], 0.8282	
RD [95%-CI]; p-value	0.04 [-0.15, 0.23], 0.6610		-0.01 [-0.20, 0.18], 0.9320		0.02 [-0.12, 0.15], 0.8267	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	15/57 (26.3)	10/32 (31.3)	16/59 (27.1)	9/36 (25.0)	31/116 (26.7)	19/68 (27.9)
RR [95%-CI]; p-value	0.84 [0.43, 1.65], 0.6167		1.08 [0.54, 2.19], 0.8207		0.96 [0.59, 1.56], 0.8576	
OR [95%-CI]; p-value	0.79 [0.30, 2.04], 0.6192		1.12 [0.43, 2.88], 0.8200		0.94 [0.48, 1.84], 0.8578	
RD [95%-CI]; p-value	-0.05 [-0.25, 0.15], 0.6237		0.02 [-0.16, 0.20], 0.8189		-0.01 [-0.15, 0.12], 0.8583	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.7712		0.7850		0.6182	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	6/58 (10.3)	3/30 (10.0)	4/60 (6.7)	1/24 (4.2)	10/118 (8.5)	4/54 (7.4)
RR [95%-CI]; p-value	1.03 [0.28, 3.85], 0.9597		1.60 [0.19, 13.59], 0.6668		1.14 [0.38, 3.49], 0.8128	
OR [95%-CI]; p-value	1.04 [0.24, 4.48], 0.9596		1.64 [0.17, 15.50], 0.6618		1.16 [0.35, 3.87], 0.8122	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9594		0.03 [-0.08, 0.13], 0.6305		0.01 [-0.08, 0.10], 0.8079	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	2/32 (6.3)	4/59 (6.8)	1/36 (2.8)	9/116 (7.8)	3/68 (4.4)
RR [95%-CI]; p-value	1.40 [0.29, 6.83], 0.6744		2.44 [0.28, 20.99], 0.4164		1.76 [0.49, 6.27], 0.3843	
OR [95%-CI]; p-value	1.44 [0.26, 7.90], 0.6715		2.55 [0.27, 23.72], 0.3968		1.82 [0.48, 6.98], 0.3748	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6575		0.04 [-0.04, 0.12], 0.3484		0.03 [-0.04, 0.10], 0.3413	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2503		0.6085		0.2470	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	9/58 (15.5)	4/30 (13.3)	7/60 (11.7)	2/24 (8.3)	16/118 (13.6)	6/54 (11.1)
RR [95%-CI]; p-value	1.16 [0.39, 3.47], 0.7855		1.40 [0.31, 6.26], 0.6599		1.22 [0.51, 2.95], 0.6579	
OR [95%-CI]; p-value	1.19 [0.34, 4.25], 0.7843		1.45 [0.28, 7.55], 0.6554		1.25 [0.46, 3.41], 0.6555	
RD [95%-CI]; p-value	0.02 [-0.13, 0.18], 0.7800		0.03 [-0.10, 0.17], 0.6340		0.02 [-0.08, 0.13], 0.6449	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	6/32 (18.8)	4/59 (6.8)	3/36 (8.3)	9/116 (7.8)	9/68 (13.2)
RR [95%-CI]; p-value	0.47 [0.15, 1.41], 0.1779		0.81 [0.19, 3.43], 0.7786		0.59 [0.24, 1.40], 0.2311	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1699		0.80 [0.17, 3.80], 0.7786		0.55 [0.21, 1.46], 0.2274	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.2038		-0.02 [-0.13, 0.10], 0.7834		-0.05 [-0.15, 0.04], 0.2541	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5948		0.7957		0.7736	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	13/58 (22.4)	9/30 (30.0)	8/60 (13.3)	3/24 (12.5)	21/118 (17.8)	12/54 (22.2)
RR [95%-CI]; p-value	0.75 [0.36, 1.55], 0.4317		1.07 [0.31, 3.68], 0.9187		0.80 [0.43, 1.51], 0.4910	
OR [95%-CI]; p-value	0.67 [0.25, 1.82], 0.4360		1.08 [0.26, 4.46], 0.9185		0.76 [0.34, 1.68], 0.4939	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.12], 0.4480		0.01 [-0.15, 0.17], 0.9176		-0.04 [-0.17, 0.09], 0.5066	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	10/57 (17.5)	10/32 (31.3)	13/59 (22.0)	9/36 (25.0)	23/116 (19.8)	19/68 (27.9)
RR [95%-CI]; p-value	0.56 [0.26, 1.20], 0.1376		0.88 [0.42, 1.85], 0.7387		0.71 [0.42, 1.20], 0.2036	
OR [95%-CI]; p-value	0.47 [0.17, 1.29], 0.1371		0.85 [0.32, 2.24], 0.7395		0.64 [0.32, 1.28], 0.2056	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1542		-0.03 [-0.21, 0.15], 0.7420		-0.08 [-0.21, 0.05], 0.2176	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3472		0.0175		0.0219	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	9/30 (30.0)	13/60 (21.7)	2/24 (8.3)	25/118 (21.2)	11/54 (20.4)
RR [95%-CI]; p-value	0.69 [0.33, 1.45], 0.3273		2.60 [0.63, 10.66], 0.1846		1.04 [0.55, 1.96], 0.9030	
OR [95%-CI]; p-value	0.61 [0.22, 1.67], 0.3314		3.04 [0.63, 14.66], 0.1495		1.05 [0.47, 2.33], 0.9028	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.10], 0.3477		0.13 [-0.02, 0.29], 0.0855		0.01 [-0.12, 0.14], 0.9023	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	11/32 (34.4)	7/59 (11.9)	12/36 (33.3)	15/116 (12.9)	23/68 (33.8)
RR [95%-CI]; p-value	0.41 [0.18, 0.91], 0.0284		0.36 [0.15, 0.82], 0.0153		0.38 [0.21, 0.68], 0.0011	
OR [95%-CI]; p-value	0.31 [0.11, 0.89], 0.0246		0.27 [0.09, 0.77], 0.0112		0.29 [0.14, 0.61], 0.0007	
RD [95%-CI]; p-value	-0.20 [-0.39, -0.02], 0.0336		-0.21 [-0.39, -0.04], 0.0160		-0.21 [-0.34, -0.08], 0.0014	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.9180		0.1935		0.4617	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	5/58 (8.6)	5/30 (16.7)	7/60 (11.7)	1/24 (4.2)	12/118 (10.2)	6/54 (11.1)
RR [95%-CI]; p-value	0.52 [0.16, 1.65], 0.2647		2.80 [0.36, 21.56], 0.3228		0.92 [0.36, 2.31], 0.8513	
OR [95%-CI]; p-value	0.47 [0.13, 1.78], 0.2596		3.04 [0.35, 26.12], 0.2901		0.91 [0.32, 2.56], 0.8515	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2984		0.08 [-0.04, 0.19], 0.1971		-0.01 [-0.11, 0.09], 0.8536	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	6/32 (18.8)	6/59 (10.2)	6/36 (16.7)	12/116 (10.3)	12/68 (17.6)
RR [95%-CI]; p-value	0.56 [0.20, 1.60], 0.2791		0.61 [0.21, 1.75], 0.3578		0.59 [0.28, 1.23], 0.1583	
OR [95%-CI]; p-value	0.51 [0.15, 1.74], 0.2757		0.57 [0.17, 1.91], 0.3551		0.54 [0.23, 1.28], 0.1557	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.3045		-0.06 [-0.21, 0.08], 0.3769		-0.07 [-0.18, 0.03], 0.1778	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4170		0.8929		0.5255	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	6/30 (20.0)	7/60 (11.7)	2/24 (8.3)	14/118 (11.9)	8/54 (14.8)
RR [95%-CI]; p-value	0.60 [0.22, 1.64], 0.3209		1.40 [0.31, 6.26], 0.6599		0.80 [0.36, 1.79], 0.5895	
OR [95%-CI]; p-value	0.55 [0.17, 1.81], 0.3203		1.45 [0.28, 7.55], 0.6554		0.77 [0.30, 1.97], 0.5908	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3487		0.03 [-0.10, 0.17], 0.6340		-0.03 [-0.14, 0.08], 0.6033	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	4/32 (12.5)	6/59 (10.2)	3/36 (8.3)	14/116 (12.1)	7/68 (10.3)
RR [95%-CI]; p-value	1.12 [0.37, 3.44], 0.8393		1.22 [0.33, 4.58], 0.7679		1.17 [0.50, 2.76], 0.7159	
OR [95%-CI]; p-value	1.14 [0.32, 4.14], 0.8388		1.25 [0.29, 5.32], 0.7669		1.20 [0.46, 3.13], 0.7148	
RD [95%-CI]; p-value	0.02 [-0.13, 0.16], 0.8365		0.02 [-0.10, 0.14], 0.7618		0.02 [-0.08, 0.11], 0.7097	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0990		0.3403		0.0226	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	0/30 (0.0)	8/60 (13.3)	2/24 (8.3)	11/118 (9.3)	2/54 (3.7)
RR [95%-CI]; p-value	3.16 [0.16, 60.99], 0.4470		1.60 [0.37, 7.00], 0.5324		2.52 [0.58, 10.97], 0.2190	
OR [95%-CI]; p-value	3.27 [0.16, 67.52], 0.4177		1.69 [0.33, 8.62], 0.5227		2.67 [0.57, 12.50], 0.1958	
RD [95%-CI]; p-value	0.04 [-0.04, 0.11], 0.3406		0.05 [-0.09, 0.19], 0.4842		0.06 [-0.02, 0.13], 0.1300	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	8/32 (25.0)	4/59 (6.8)	4/36 (11.1)	7/116 (6.0)	12/68 (17.6)
RR [95%-CI]; p-value	0.21 [0.06, 0.74], 0.0149		0.61 [0.16, 2.29], 0.4641		0.34 [0.14, 0.83], 0.0172	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0066		0.58 [0.14, 2.49], 0.4608		0.30 [0.11, 0.80], 0.0125	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0162		-0.04 [-0.16, 0.08], 0.4831		-0.12 [-0.22, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7689		0.6603		0.9926	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	3/30 (10.0)	3/60 (5.0)	2/24 (8.3)	7/118 (5.9)	5/54 (9.3)
RR [95%-CI]; p-value	0.69 [0.16, 2.88], 0.6107		0.60 [0.11, 3.37], 0.5617		0.64 [0.21, 1.93], 0.4282	
OR [95%-CI]; p-value	0.67 [0.14, 3.19], 0.6101		0.58 [0.09, 3.70], 0.5597		0.62 [0.19, 2.04], 0.4267	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6282		-0.03 [-0.16, 0.09], 0.5970		-0.03 [-0.12, 0.06], 0.4601	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	5/32 (15.6)	3/59 (5.1)	5/36 (13.9)	11/116 (9.5)	10/68 (14.7)
RR [95%-CI]; p-value	0.90 [0.32, 2.52], 0.8382		0.37 [0.09, 1.44], 0.1506		0.64 [0.29, 1.44], 0.2838	
OR [95%-CI]; p-value	0.88 [0.26, 2.96], 0.8385		0.33 [0.07, 1.48], 0.1339		0.61 [0.24, 1.52], 0.2821	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8404		-0.09 [-0.21, 0.04], 0.1712		-0.05 [-0.15, 0.05], 0.3042	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.4.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3457		0.8458		0.4349	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	6/30 (20.0)	3/60 (5.0)	0/24 (0.0)	4/118 (3.4)	6/54 (11.1)
RR [95%-CI]; p-value	0.09 [0.01, 0.68], 0.0203		2.45 [0.13, 47.13], 0.5525		0.31 [0.09, 1.04], 0.0572	
OR [95%-CI]; p-value	0.07 [0.01, 0.61], 0.0027		2.53 [0.12, 52.37], 0.5356		0.28 [0.08, 1.04], 0.0446	
RD [95%-CI]; p-value	-0.18 [-0.33, -0.04], 0.0148		0.03 [-0.05, 0.11], 0.4605		-0.08 [-0.17, 0.01], 0.0925	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	6/32 (18.8)	3/59 (5.1)	0/36 (0.0)	6/116 (5.2)	6/68 (8.8)
RR [95%-CI]; p-value	0.28 [0.08, 1.05], 0.0586		3.71 [0.19, 72.01], 0.3860		0.59 [0.20, 1.75], 0.3374	
OR [95%-CI]; p-value	0.24 [0.06, 1.04], 0.0429		3.86 [0.19, 79.28], 0.3478		0.56 [0.17, 1.82], 0.3329	
RD [95%-CI]; p-value	-0.13 [-0.28, 0.01], 0.0724		0.04 [-0.03, 0.10], 0.2812		-0.04 [-0.12, 0.04], 0.3622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_4_m_pt_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.7662		0.4741		0.4674	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	2/30 (6.7)	3/60 (5.0)	1/24 (4.2)	11/118 (9.3)	3/54 (5.6)
RR [95%-CI]; p-value	2.07 [0.47, 9.14], 0.3374		1.20 [0.13, 10.97], 0.8717		1.68 [0.49, 5.77], 0.4115	
OR [95%-CI]; p-value	2.24 [0.44, 11.29], 0.3180		1.21 [0.12, 12.25], 0.8713		1.75 [0.47, 6.54], 0.4018	
RD [95%-CI]; p-value	0.07 [-0.05, 0.20], 0.2671		0.01 [-0.09, 0.11], 0.8664		0.04 [-0.04, 0.12], 0.3593	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	0/32 (0.0)	3/59 (5.1)	4/36 (11.1)	6/116 (5.2)	4/68 (5.9)
RR [95%-CI]; p-value	3.42 [0.18, 66.20], 0.4158		0.46 [0.11, 1.93], 0.2868		0.88 [0.26, 3.01], 0.8375	
OR [95%-CI]; p-value	3.56 [0.17, 73.27], 0.3820		0.43 [0.09, 2.04], 0.2754		0.87 [0.24, 3.21], 0.8375	
RD [95%-CI]; p-value	0.04 [-0.03, 0.11], 0.3091		-0.06 [-0.18, 0.06], 0.3126		-0.01 [-0.08, 0.06], 0.8400	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7658		NA		0.7205	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	0/58 (0.0)	0/30 (0.0)	0/60 (0.0)	0/24 (0.0)	0/118 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	1/116 (0.9)	0/68 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.07], 0.9391		NA		1.18 [0.04, 34.74], 0.9232	
OR [95%-CI]; p-value	1.14 [0.04, 35.02], 0.9390		NA		1.18 [0.04, 35.72], 0.9231	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9379		NA		0.00 [-0.02, 0.03], 0.9214	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9553		0.4741		0.3614	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	2/30 (6.7)	3/60 (5.0)	1/24 (4.2)	11/118 (9.3)	3/54 (5.6)
RR [95%-CI]; p-value	2.07 [0.47, 9.14], 0.3374		1.20 [0.13, 10.97], 0.8717		1.68 [0.49, 5.77], 0.4115	
OR [95%-CI]; p-value	2.24 [0.44, 11.29], 0.3180		1.21 [0.12, 12.25], 0.8713		1.75 [0.47, 6.54], 0.4018	
RD [95%-CI]; p-value	0.07 [-0.05, 0.20], 0.2671		0.01 [-0.09, 0.11], 0.8664		0.04 [-0.04, 0.12], 0.3593	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	2/57 (3.5)	0/32 (0.0)	3/59 (5.1)	4/36 (11.1)	5/116 (4.3)	4/68 (5.9)
RR [95%-CI]; p-value	2.28 [0.11, 49.08], 0.5985		0.46 [0.11, 1.93], 0.2868		0.73 [0.20, 2.64], 0.6341	
OR [95%-CI]; p-value	2.33 [0.10, 53.21], 0.5864		0.43 [0.09, 2.04], 0.2754		0.72 [0.19, 2.78], 0.6332	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5451		-0.06 [-0.18, 0.06], 0.3126		-0.02 [-0.08, 0.05], 0.6458	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.7700		0.9132		0.7454	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	1/30 (3.3)	1/60 (1.7)	0/24 (0.0)	5/118 (4.2)	1/54 (1.9)
RR [95%-CI]; p-value	2.07 [0.24, 17.70], 0.5068		0.82 [0.03, 23.56], 0.9060		2.29 [0.27, 19.12], 0.4447	
OR [95%-CI]; p-value	2.15 [0.23, 20.12], 0.4937		0.81 [0.03, 25.06], 0.9059		2.35 [0.27, 20.57], 0.4288	
RD [95%-CI]; p-value	0.04 [-0.06, 0.13], 0.4455		-0.00 [-0.07, 0.06], 0.9097		0.02 [-0.03, 0.07], 0.3605	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	1/116 (0.9)	0/68 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.07], 0.9391		NA		1.18 [0.04, 34.74], 0.9232	
OR [95%-CI]; p-value	1.14 [0.04, 35.02], 0.9390		NA		1.18 [0.04, 35.72], 0.9231	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9379		NA		0.00 [-0.02, 0.03], 0.9214	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7629		0.1703		0.2469	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	4/30 (13.3)	3/60 (5.0)	3/24 (12.5)	7/118 (5.9)	7/54 (13.0)
RR [95%-CI]; p-value	0.52 [0.14, 1.92], 0.3254		0.40 [0.09, 1.84], 0.2401		0.46 [0.17, 1.24], 0.1243	
OR [95%-CI]; p-value	0.48 [0.11, 2.08], 0.3194		0.37 [0.07, 1.97], 0.2279		0.42 [0.14, 1.27], 0.1176	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.07], 0.3607		-0.08 [-0.22, 0.07], 0.3051		-0.07 [-0.17, 0.03], 0.1648	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	5/32 (15.6)	6/59 (10.2)	2/36 (5.6)	12/116 (10.3)	7/68 (10.3)
RR [95%-CI]; p-value	0.67 [0.22, 2.03], 0.4836		1.83 [0.39, 8.59], 0.4433		1.00 [0.42, 2.43], 0.9913	
OR [95%-CI]; p-value	0.64 [0.18, 2.27], 0.4831		1.92 [0.37, 10.09], 0.4321		1.01 [0.38, 2.69], 0.9913	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.10], 0.5022		0.05 [-0.06, 0.15], 0.4000		0.00 [-0.09, 0.09], 0.9913	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8131		0.2773		0.4365	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	0/30 (0.0)	0/60 (0.0)	1/24 (4.2)	1/118 (0.8)	1/54 (1.9)
RR [95%-CI]; p-value	1.05 [0.04, 30.47], 0.9766		0.20 [0.01, 5.72], 0.3456		0.46 [0.03, 7.18], 0.5779	
OR [95%-CI]; p-value	1.05 [0.03, 32.29], 0.9766		0.19 [0.01, 5.91], 0.2944		0.45 [0.03, 7.38], 0.5685	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9764		-0.03 [-0.12, 0.05], 0.4310		-0.01 [-0.05, 0.03], 0.6189	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	0/57 (0.0)	0/32 (0.0)	2/59 (3.4)	0/36 (0.0)	2/116 (1.7)	0/68 (0.0)
RR [95%-CI]; p-value	NA		2.47 [0.11, 53.38], 0.5631		2.36 [0.11, 51.63], 0.5850	
OR [95%-CI]; p-value	NA		2.53 [0.11, 57.61], 0.5480		2.39 [0.11, 53.68], 0.5725	
RD [95%-CI]; p-value	NA		0.02 [-0.04, 0.08], 0.5066		0.01 [-0.02, 0.04], 0.5310	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.5496		0.2337		0.2240	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	4/30 (13.3)	3/60 (5.0)	3/24 (12.5)	6/118 (5.1)	7/54 (13.0)
RR [95%-CI]; p-value	0.39 [0.09, 1.62], 0.1945		0.40 [0.09, 1.84], 0.2401		0.39 [0.14, 1.11], 0.0783	
OR [95%-CI]; p-value	0.35 [0.07, 1.70], 0.1799		0.37 [0.07, 1.97], 0.2279		0.36 [0.11, 1.13], 0.0697	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2338		-0.08 [-0.22, 0.07], 0.3051		-0.08 [-0.18, 0.02], 0.1150	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	5/32 (15.6)	5/59 (8.5)	2/36 (5.6)	11/116 (9.5)	7/68 (10.3)
RR [95%-CI]; p-value	0.67 [0.22, 2.03], 0.4836		1.53 [0.31, 7.45], 0.6019		0.92 [0.37, 2.26], 0.8580	
OR [95%-CI]; p-value	0.64 [0.18, 2.27], 0.4831		1.57 [0.29, 8.57], 0.5973		0.91 [0.34, 2.48], 0.8581	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.10], 0.5022		0.03 [-0.07, 0.13], 0.5793		-0.01 [-0.10, 0.08], 0.8594	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9708		0.3848		0.5109	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	2/58 (3.4)	0/30 (0.0)	1/60 (1.7)	1/24 (4.2)	3/118 (2.5)	1/54 (1.9)
RR [95%-CI]; p-value	2.10 [0.10, 45.21], 0.6347		0.40 [0.03, 6.14], 0.5108		1.37 [0.15, 12.90], 0.7816	
OR [95%-CI]; p-value	2.14 [0.09, 49.04], 0.6255		0.39 [0.02, 6.50], 0.4972		1.38 [0.14, 13.60], 0.7803	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.5859		-0.03 [-0.11, 0.06], 0.5700		0.01 [-0.04, 0.05], 0.7677	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	2/57 (3.5)	0/32 (0.0)	2/59 (3.4)	0/36 (0.0)	4/116 (3.4)	0/68 (0.0)
RR [95%-CI]; p-value	2.28 [0.11, 49.08], 0.5985		2.47 [0.11, 53.38], 0.5631		4.72 [0.25, 88.01], 0.2981	
OR [95%-CI]; p-value	2.33 [0.10, 53.21], 0.5864		2.53 [0.11, 57.61], 0.5480		4.86 [0.25, 93.30], 0.2475	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5451		0.02 [-0.04, 0.08], 0.5066		0.03 [-0.01, 0.07], 0.1702	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.6.s3.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.9704		0.3202		0.7025	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	7/30 (23.3)	10/60 (16.7)	1/24 (4.2)	17/118 (14.4)	8/54 (14.8)
RR [95%-CI]; p-value	0.52 [0.20, 1.34], 0.1740		4.00 [0.54, 29.57], 0.1744		0.97 [0.45, 2.11], 0.9438	
OR [95%-CI]; p-value	0.45 [0.14, 1.44], 0.1709		4.60 [0.56, 38.10], 0.1250		0.97 [0.39, 2.40], 0.9438	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.06], 0.2019		0.13 [0.00, 0.25], 0.0475		-0.00 [-0.12, 0.11], 0.9441	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	9/57 (15.8)	10/32 (31.3)	13/59 (22.0)	6/36 (16.7)	22/116 (19.0)	16/68 (23.5)
RR [95%-CI]; p-value	0.51 [0.23, 1.11], 0.0902		1.32 [0.55, 3.17], 0.5313		0.81 [0.46, 1.43], 0.4586	
OR [95%-CI]; p-value	0.41 [0.15, 1.16], 0.0876		1.41 [0.48, 4.12], 0.5258		0.76 [0.37, 1.57], 0.4604	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.03], 0.1041		0.05 [-0.11, 0.21], 0.5142		-0.05 [-0.17, 0.08], 0.4689	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_6_m_pt_adr_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.0464		0.7915		0.2215	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	48/65 (73.8)	30/41 (73.2)	53/83 (63.9)	25/39 (64.1)	101/148 (68.2)	55/80 (68.8)
RR [95%-CI]; p-value	1.01 [0.80, 1.28], 0.9389		1.00 [0.75, 1.32], 0.9788		0.99 [0.83, 1.19], 0.9372	
OR [95%-CI]; p-value	1.04 [0.43, 2.51], 0.9388		0.99 [0.45, 2.19], 0.9788		0.98 [0.54, 1.75], 0.9374	
RD [95%-CI]; p-value	0.01 [-0.17, 0.18], 0.9389		-0.00 [-0.19, 0.18], 0.9788		-0.01 [-0.13, 0.12], 0.9373	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	35/50 (70.0)	20/21 (95.2)	19/36 (52.8)	12/21 (57.1)	54/86 (62.8)	32/42 (76.2)
RR [95%-CI]; p-value	0.74 [0.60, 0.90], 0.0033		0.92 [0.57, 1.50], 0.7468		0.82 [0.65, 1.04], 0.1061	
OR [95%-CI]; p-value	0.12 [0.01, 0.95], 0.0202		0.84 [0.28, 2.48], 0.7496		0.53 [0.23, 1.21], 0.1295	
RD [95%-CI]; p-value	-0.25 [-0.41, -0.10], 0.0016		-0.04 [-0.31, 0.22], 0.7488		-0.13 [-0.30, 0.03], 0.1102	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.7280		0.2784		0.1762	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	7/41 (17.1)	6/83 (7.2)	2/39 (5.1)	13/148 (8.8)	9/80 (11.3)
RR [95%-CI]; p-value	0.63 [0.24, 1.67], 0.3528		1.41 [0.30, 6.67], 0.6651		0.78 [0.35, 1.75], 0.5469	
OR [95%-CI]; p-value	0.59 [0.19, 1.81], 0.3505		1.44 [0.28, 7.49], 0.6620		0.76 [0.31, 1.86], 0.5472	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.07], 0.3694		0.02 [-0.07, 0.11], 0.6431		-0.02 [-0.11, 0.06], 0.5599	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	3/21 (14.3)	7/36 (19.4)	0/21 (0.0)	13/86 (15.1)	3/42 (7.1)
RR [95%-CI]; p-value	0.84 [0.23, 3.05], 0.7909		8.36 [0.50, 140.12], 0.1398		2.12 [0.64, 7.03], 0.2208	
OR [95%-CI]; p-value	0.82 [0.18, 3.63], 0.7916		10.14 [0.54, 188.64], 0.0622		2.32 [0.62, 8.62], 0.2003	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7976		0.17 [0.03, 0.32], 0.0199		0.08 [-0.03, 0.19], 0.1502	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.4116		0.5538		0.7540	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	5/65 (7.7)	3/41 (7.3)	2/83 (2.4)	2/39 (5.1)	7/148 (4.7)	5/80 (6.3)
RR [95%-CI]; p-value	1.05 [0.27, 4.17], 0.9433		0.47 [0.07, 3.21], 0.4413		0.76 [0.25, 2.31], 0.6242	
OR [95%-CI]; p-value	1.06 [0.24, 4.67], 0.9432		0.46 [0.06, 3.37], 0.4317		0.74 [0.23, 2.43], 0.6237	
RD [95%-CI]; p-value	0.00 [-0.10, 0.11], 0.9429		-0.03 [-0.10, 0.05], 0.4872		-0.02 [-0.08, 0.05], 0.6368	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	1/21 (4.8)	1/36 (2.8)	3/21 (14.3)	8/86 (9.3)	4/42 (9.5)
RR [95%-CI]; p-value	2.94 [0.39, 22.44], 0.2983		0.19 [0.02, 1.75], 0.1443		0.98 [0.31, 3.06], 0.9678	
OR [95%-CI]; p-value	3.26 [0.37, 28.27], 0.2612		0.17 [0.02, 1.77], 0.1009		0.97 [0.28, 3.44], 0.9678	
RD [95%-CI]; p-value	0.09 [-0.04, 0.22], 0.1717		-0.12 [-0.27, 0.04], 0.1560		-0.00 [-0.11, 0.11], 0.9679	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.7803		0.5740		0.4971	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	9/65 (13.8)	6/41 (14.6)	6/83 (7.2)	4/39 (10.3)	15/148 (10.1)	10/80 (12.5)
RR [95%-CI]; p-value	0.95 [0.36, 2.46], 0.9097		0.70 [0.21, 2.36], 0.5699		0.81 [0.38, 1.72], 0.5849	
OR [95%-CI]; p-value	0.94 [0.31, 2.86], 0.9097		0.68 [0.18, 2.57], 0.5697		0.79 [0.34, 1.85], 0.5855	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.13], 0.9102		-0.03 [-0.14, 0.08], 0.5907		-0.02 [-0.11, 0.06], 0.5953	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	11/50 (22.0)	4/21 (19.0)	6/36 (16.7)	3/21 (14.3)	17/86 (19.8)	7/42 (16.7)
RR [95%-CI]; p-value	1.16 [0.41, 3.22], 0.7828		1.17 [0.33, 4.18], 0.8130		1.19 [0.53, 2.64], 0.6756	
OR [95%-CI]; p-value	1.20 [0.33, 4.30], 0.7809		1.20 [0.27, 5.40], 0.8120		1.23 [0.47, 3.25], 0.6730	
RD [95%-CI]; p-value	0.03 [-0.17, 0.23], 0.7761		0.02 [-0.17, 0.22], 0.8089		0.03 [-0.11, 0.17], 0.6657	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.2458		0.7710		0.4738	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	5/65 (7.7)	1/41 (2.4)	2/83 (2.4)	0/39 (0.0)	7/148 (4.7)	1/80 (1.3)
RR [95%-CI]; p-value	3.15 [0.38, 26.04], 0.2863		1.90 [0.09, 41.24], 0.6816		3.78 [0.47, 30.21], 0.2093	
OR [95%-CI]; p-value	3.33 [0.38, 29.61], 0.2543		1.93 [0.08, 43.72], 0.6756		3.92 [0.47, 32.46], 0.1729	
RD [95%-CI]; p-value	0.05 [-0.03, 0.13], 0.1990		0.01 [-0.04, 0.06], 0.6405		0.03 [-0.01, 0.08], 0.1042	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	3/50 (6.0)	2/21 (9.5)	3/36 (8.3)	0/21 (0.0)	6/86 (7.0)	2/42 (4.8)
RR [95%-CI]; p-value	0.63 [0.11, 3.50], 0.5975		3.58 [0.19, 68.18], 0.3958		1.47 [0.31, 6.95], 0.6307	
OR [95%-CI]; p-value	0.61 [0.09, 3.92], 0.5964		3.82 [0.18, 80.10], 0.3566		1.50 [0.29, 7.77], 0.6269	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6261		0.06 [-0.05, 0.17], 0.2866		0.02 [-0.06, 0.11], 0.6051	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8655		NA		0.9659	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	0/41 (0.0)	0/83 (0.0)	0/39 (0.0)	0/148 (0.0)	0/80 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	1/21 (4.8)	0/36 (0.0)	0/21 (0.0)	1/86 (1.2)	1/42 (2.4)
RR [95%-CI]; p-value	0.42 [0.03, 6.40], 0.5326		NA		0.49 [0.03, 7.62], 0.6091	
OR [95%-CI]; p-value	0.41 [0.02, 6.85], 0.5209		NA		0.48 [0.03, 7.91], 0.6018	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.5845		NA		-0.01 [-0.06, 0.04], 0.6421	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.9067		NA		0.8196	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	1/41 (2.4)	0/83 (0.0)	0/39 (0.0)	0/148 (0.0)	1/80 (1.3)
RR [95%-CI]; p-value	0.31 [0.01, 9.12], 0.4996		NA		0.27 [0.01, 7.94], 0.4474	
OR [95%-CI]; p-value	0.31 [0.01, 9.38], 0.4752		NA		0.27 [0.01, 8.04], 0.4148	
RD [95%-CI]; p-value	-0.02 [-0.07, 0.03], 0.5253		NA		-0.01 [-0.04, 0.02], 0.4923	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	0/50 (0.0)	0/21 (0.0)	0/36 (0.0)	0/21 (0.0)	0/86 (0.0)	0/42 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.0329		0.6555		0.3217	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	40/65 (61.5)	26/41 (63.4)	44/83 (53.0)	21/39 (53.8)	84/148 (56.8)	47/80 (58.8)
RR [95%-CI]; p-value	0.97 [0.72, 1.31], 0.8453		0.98 [0.69, 1.40], 0.9312		0.97 [0.77, 1.22], 0.7699	
OR [95%-CI]; p-value	0.92 [0.41, 2.07], 0.8461		0.97 [0.45, 2.07], 0.9314		0.92 [0.53, 1.60], 0.7714	
RD [95%-CI]; p-value	-0.02 [-0.21, 0.17], 0.8457		-0.01 [-0.20, 0.18], 0.9313		-0.02 [-0.15, 0.11], 0.7710	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	28/50 (56.0)	19/21 (90.5)	16/36 (44.4)	8/21 (38.1)	44/86 (51.2)	27/42 (64.3)
RR [95%-CI]; p-value	0.62 [0.47, 0.82], 0.0009		1.17 [0.61, 2.25], 0.6452		0.80 [0.59, 1.08], 0.1432	
OR [95%-CI]; p-value	0.13 [0.03, 0.64], 0.0051		1.30 [0.43, 3.90], 0.6395		0.58 [0.27, 1.24], 0.1607	
RD [95%-CI]; p-value	-0.34 [-0.53, -0.16], 0.0003		0.06 [-0.20, 0.33], 0.6369		-0.13 [-0.31, 0.05], 0.1515	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.8524		0.3514		0.5201	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	23/65 (35.4)	17/41 (41.5)	24/83 (28.9)	8/39 (20.5)	47/148 (31.8)	25/80 (31.3)
RR [95%-CI]; p-value	0.85 [0.52, 1.39], 0.5261		1.41 [0.70, 2.85], 0.3391		1.02 [0.68, 1.52], 0.9375	
OR [95%-CI]; p-value	0.77 [0.35, 1.73], 0.5295		1.58 [0.63, 3.92], 0.3251		1.02 [0.57, 1.84], 0.9374	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5315		0.08 [-0.08, 0.24], 0.3031		0.01 [-0.12, 0.13], 0.9373	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	15/50 (30.0)	8/21 (38.1)	12/36 (33.3)	8/21 (38.1)	27/86 (31.4)	16/42 (38.1)
RR [95%-CI]; p-value	0.79 [0.39, 1.57], 0.4976		0.88 [0.43, 1.79], 0.7142		0.82 [0.50, 1.35], 0.4449	
OR [95%-CI]; p-value	0.70 [0.24, 2.03], 0.5059		0.81 [0.26, 2.49], 0.7163		0.74 [0.34, 1.61], 0.4511	
RD [95%-CI]; p-value	-0.08 [-0.32, 0.16], 0.5146		-0.05 [-0.31, 0.21], 0.7181		-0.07 [-0.24, 0.11], 0.4572	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.4116		0.5538		0.7540	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	5/65 (7.7)	3/41 (7.3)	2/83 (2.4)	2/39 (5.1)	7/148 (4.7)	5/80 (6.3)
RR [95%-CI]; p-value	1.05 [0.27, 4.17], 0.9433		0.47 [0.07, 3.21], 0.4413		0.76 [0.25, 2.31], 0.6242	
OR [95%-CI]; p-value	1.06 [0.24, 4.67], 0.9432		0.46 [0.06, 3.37], 0.4317		0.74 [0.23, 2.43], 0.6237	
RD [95%-CI]; p-value	0.00 [-0.10, 0.11], 0.9429		-0.03 [-0.10, 0.05], 0.4872		-0.02 [-0.08, 0.05], 0.6368	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	1/21 (4.8)	1/36 (2.8)	3/21 (14.3)	8/86 (9.3)	4/42 (9.5)
RR [95%-CI]; p-value	2.94 [0.39, 22.44], 0.2983		0.19 [0.02, 1.75], 0.1443		0.98 [0.31, 3.06], 0.9678	
OR [95%-CI]; p-value	3.26 [0.37, 28.27], 0.2612		0.17 [0.02, 1.77], 0.1009		0.97 [0.28, 3.44], 0.9678	
RD [95%-CI]; p-value	0.09 [-0.04, 0.22], 0.1717		-0.12 [-0.27, 0.04], 0.1560		-0.00 [-0.11, 0.11], 0.9679	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.8415		0.7485		0.7783	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	5/41 (12.2)	3/83 (3.6)	1/39 (2.6)	7/148 (4.7)	6/80 (7.5)
RR [95%-CI]; p-value	0.50 [0.14, 1.77], 0.2856		1.41 [0.15, 13.12], 0.7629		0.63 [0.22, 1.81], 0.3921	
OR [95%-CI]; p-value	0.47 [0.12, 1.87], 0.2772		1.43 [0.14, 14.15], 0.7613		0.61 [0.20, 1.89], 0.3893	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3072		0.01 [-0.05, 0.07], 0.7470		-0.03 [-0.09, 0.04], 0.4183	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	4/50 (8.0)	4/21 (19.0)	4/36 (11.1)	1/21 (4.8)	8/86 (9.3)	5/42 (11.9)
RR [95%-CI]; p-value	0.42 [0.12, 1.52], 0.1871		2.33 [0.28, 19.52], 0.4343		0.78 [0.27, 2.24], 0.6467	
OR [95%-CI]; p-value	0.37 [0.08, 1.65], 0.1791		2.50 [0.26, 23.99], 0.4137		0.76 [0.23, 2.48], 0.6472	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2393		0.06 [-0.07, 0.20], 0.3645		-0.03 [-0.14, 0.09], 0.6590	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4423		0.1555		0.1997	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	11/41 (26.8)	16/83 (19.3)	2/39 (5.1)	29/148 (19.6)	13/80 (16.3)
RR [95%-CI]; p-value	0.75 [0.37, 1.50], 0.4117		3.76 [0.91, 15.55], 0.0676		1.21 [0.67, 2.19], 0.5375	
OR [95%-CI]; p-value	0.68 [0.27, 1.71], 0.4132		4.42 [0.96, 20.28], 0.0399		1.26 [0.61, 2.58], 0.5341	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.10], 0.4225		0.14 [0.03, 0.25], 0.0113		0.03 [-0.07, 0.14], 0.5248	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	8/50 (16.0)	7/21 (33.3)	7/36 (19.4)	4/21 (19.0)	15/86 (17.4)	11/42 (26.2)
RR [95%-CI]; p-value	0.48 [0.20, 1.15], 0.1010		1.02 [0.34, 3.08], 0.9708		0.67 [0.34, 1.32], 0.2447	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1025		1.03 [0.26, 4.02], 0.9708		0.60 [0.25, 1.44], 0.2480	
RD [95%-CI]; p-value	-0.17 [-0.40, 0.05], 0.1324		0.00 [-0.21, 0.22], 0.9707		-0.09 [-0.24, 0.07], 0.2695	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8217		0.5654		0.5665	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	10/41 (24.4)	9/83 (10.8)	5/39 (12.8)	17/148 (11.5)	15/80 (18.8)
RR [95%-CI]; p-value	0.50 [0.22, 1.17], 0.1120		0.85 [0.30, 2.36], 0.7487		0.61 [0.32, 1.16], 0.1327	
OR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1066		0.83 [0.26, 2.65], 0.7493		0.56 [0.26, 1.20], 0.1318	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.03], 0.1236		-0.02 [-0.14, 0.10], 0.7555		-0.07 [-0.17, 0.03], 0.1536	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	5/21 (23.8)	5/36 (13.9)	2/21 (9.5)	12/86 (14.0)	7/42 (16.7)
RR [95%-CI]; p-value	0.59 [0.21, 1.64], 0.3114		1.46 [0.31, 6.86], 0.6331		0.84 [0.36, 1.97], 0.6841	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3141		1.53 [0.27, 8.70], 0.6281		0.81 [0.29, 2.24], 0.6852	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3506		0.04 [-0.13, 0.21], 0.6125		-0.03 [-0.16, 0.11], 0.6924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.6268		0.3277		0.3324	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	19/65 (29.2)	11/41 (26.8)	21/83 (25.3)	8/39 (20.5)	40/148 (27.0)	19/80 (23.8)
RR [95%-CI]; p-value	1.09 [0.58, 2.05], 0.7901		1.23 [0.60, 2.53], 0.5679		1.14 [0.71, 1.83], 0.5927	
OR [95%-CI]; p-value	1.13 [0.47, 2.70], 0.7892		1.31 [0.52, 3.30], 0.5623		1.19 [0.63, 2.23], 0.5897	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7879		0.05 [-0.11, 0.21], 0.5513		0.03 [-0.08, 0.15], 0.5848	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	12/50 (24.0)	6/21 (28.6)	7/36 (19.4)	6/21 (28.6)	19/86 (22.1)	12/42 (28.6)
RR [95%-CI]; p-value	0.84 [0.36, 1.94], 0.6831		0.68 [0.26, 1.76], 0.4264		0.77 [0.42, 1.44], 0.4173	
OR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6861		0.60 [0.17, 2.12], 0.4283		0.71 [0.31, 1.64], 0.4218	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.18], 0.6925		-0.09 [-0.32, 0.14], 0.4416		-0.06 [-0.23, 0.10], 0.4341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.9987		0.1455		0.2915	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	5/83 (6.0)	4/39 (10.3)	12/148 (8.1)	10/80 (12.5)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.59 [0.17, 2.07], 0.4073		0.65 [0.29, 1.43], 0.2852	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.56 [0.14, 2.22], 0.4043		0.62 [0.25, 1.50], 0.2838	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.04 [-0.15, 0.07], 0.4429		-0.04 [-0.13, 0.04], 0.3099	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	1/21 (4.8)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		3.50 [0.45, 27.12], 0.2304		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		4.00 [0.45, 35.79], 0.1865		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.12 [-0.03, 0.27], 0.1249		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8524		0.7540		0.6823	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	13/41 (31.7)	14/83 (16.9)	8/39 (20.5)	27/148 (18.2)	21/80 (26.3)
RR [95%-CI]; p-value	0.63 [0.33, 1.22], 0.1724		0.82 [0.38, 1.80], 0.6234		0.69 [0.42, 1.15], 0.1548	
OR [95%-CI]; p-value	0.54 [0.22, 1.32], 0.1725		0.79 [0.30, 2.07], 0.6253		0.63 [0.33, 1.20], 0.1570	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1834		-0.04 [-0.19, 0.11], 0.6342		-0.08 [-0.19, 0.03], 0.1714	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	10/50 (20.0)	6/21 (28.6)	7/36 (19.4)	4/21 (19.0)	17/86 (19.8)	10/42 (23.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.68], 0.4240		1.02 [0.34, 3.08], 0.9708		0.83 [0.42, 1.65], 0.5963	
OR [95%-CI]; p-value	0.63 [0.19, 2.02], 0.4302		1.03 [0.26, 4.02], 0.9708		0.79 [0.32, 1.91], 0.5987	
RD [95%-CI]; p-value	-0.09 [-0.31, 0.14], 0.4508		0.00 [-0.21, 0.22], 0.9707		-0.04 [-0.19, 0.11], 0.6066	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0292		0.6230		0.2304	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	14/65 (21.5)	10/41 (24.4)	11/83 (13.3)	8/39 (20.5)	25/148 (16.9)	18/80 (22.5)
RR [95%-CI]; p-value	0.88 [0.43, 1.80], 0.7318		0.65 [0.28, 1.48], 0.3008		0.75 [0.44, 1.29], 0.2993	
OR [95%-CI]; p-value	0.85 [0.34, 2.15], 0.7326		0.59 [0.22, 1.61], 0.3024		0.70 [0.36, 1.38], 0.3016	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.14], 0.7350		-0.07 [-0.22, 0.07], 0.3305		-0.06 [-0.17, 0.05], 0.3160	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	10/21 (47.6)	9/36 (25.0)	6/21 (28.6)	15/86 (17.4)	16/42 (38.1)
RR [95%-CI]; p-value	0.25 [0.11, 0.60], 0.0020		0.88 [0.36, 2.11], 0.7666		0.46 [0.25, 0.83], 0.0107	
OR [95%-CI]; p-value	0.15 [0.04, 0.50], 0.0010		0.83 [0.25, 2.80], 0.7677		0.34 [0.15, 0.79], 0.0104	
RD [95%-CI]; p-value	-0.36 [-0.59, -0.12], 0.0026		-0.04 [-0.28, 0.20], 0.7700		-0.21 [-0.37, -0.04], 0.0156	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.0801		0.6920		0.1021	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	9/41 (22.0)	7/83 (8.4)	4/39 (10.3)	11/148 (7.4)	13/80 (16.3)
RR [95%-CI]; p-value	0.28 [0.09, 0.85], 0.0249		0.82 [0.26, 2.64], 0.7427		0.46 [0.21, 0.97], 0.0424	
OR [95%-CI]; p-value	0.23 [0.07, 0.82], 0.0157		0.81 [0.22, 2.93], 0.7431		0.41 [0.18, 0.97], 0.0384	
RD [95%-CI]; p-value	-0.16 [-0.30, -0.02], 0.0265		-0.02 [-0.13, 0.09], 0.7507		-0.09 [-0.18, 0.00], 0.0581	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	2/21 (9.5)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	1.47 [0.33, 6.50], 0.6115		1.17 [0.33, 4.18], 0.8130		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	1.55 [0.29, 8.15], 0.6049		1.20 [0.27, 5.40], 0.8120		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	0.04 [-0.11, 0.20], 0.5791		0.02 [-0.17, 0.22], 0.8089		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.6713		0.9087		0.9169	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	5/41 (12.2)	3/83 (3.6)	1/39 (2.6)	6/148 (4.1)	6/80 (7.5)
RR [95%-CI]; p-value	0.38 [0.10, 1.50], 0.1667		1.41 [0.15, 13.12], 0.7629		0.54 [0.18, 1.62], 0.2723	
OR [95%-CI]; p-value	0.35 [0.08, 1.54], 0.1502		1.43 [0.14, 14.15], 0.7613		0.52 [0.16, 1.67], 0.2661	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.04], 0.1863		0.01 [-0.05, 0.07], 0.7470		-0.03 [-0.10, 0.03], 0.3053	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	2/21 (9.5)	2/36 (5.6)	1/21 (4.8)	3/86 (3.5)	3/42 (7.1)
RR [95%-CI]; p-value	0.21 [0.02, 2.19], 0.1922		1.17 [0.11, 12.10], 0.8972		0.49 [0.10, 2.32], 0.3670	
OR [95%-CI]; p-value	0.19 [0.02, 2.27], 0.1504		1.18 [0.10, 13.81], 0.8970		0.47 [0.09, 2.43], 0.3584	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.06], 0.2618		0.01 [-0.11, 0.13], 0.8950		-0.04 [-0.12, 0.05], 0.4104	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8592		0.7351		0.8525	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	6/41 (14.6)	7/83 (8.4)	2/39 (5.1)	15/148 (10.1)	8/80 (10.0)
RR [95%-CI]; p-value	0.84 [0.31, 2.25], 0.7301		1.64 [0.36, 7.55], 0.5225		1.01 [0.45, 2.29], 0.9742	
OR [95%-CI]; p-value	0.82 [0.26, 2.56], 0.7304		1.70 [0.34, 8.61], 0.5148		1.02 [0.41, 2.51], 0.9742	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.11], 0.7345		0.03 [-0.06, 0.12], 0.4788		0.00 [-0.08, 0.08], 0.9742	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	7/42 (16.7)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		1.17 [0.33, 4.18], 0.8130		0.91 [0.39, 2.10], 0.8201	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		1.20 [0.27, 5.40], 0.8120		0.89 [0.33, 2.43], 0.8206	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.02 [-0.17, 0.22], 0.8089		-0.02 [-0.15, 0.12], 0.8229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5320		0.8298		0.6179	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	6/41 (14.6)	8/83 (9.6)	4/39 (10.3)	11/148 (7.4)	10/80 (12.5)
RR [95%-CI]; p-value	0.32 [0.08, 1.19], 0.0889		0.94 [0.30, 2.93], 0.9148		0.59 [0.26, 1.34], 0.2096	
OR [95%-CI]; p-value	0.28 [0.07, 1.20], 0.0715		0.93 [0.26, 3.31], 0.9149		0.56 [0.23, 1.39], 0.2066	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.02], 0.1007		-0.01 [-0.12, 0.11], 0.9157		-0.05 [-0.13, 0.03], 0.2364	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	3/50 (6.0)	2/21 (9.5)	4/36 (11.1)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	0.63 [0.11, 3.50], 0.5975		1.17 [0.23, 5.84], 0.8511		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	0.61 [0.09, 3.92], 0.5964		1.19 [0.20, 7.11], 0.8506		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6261		0.02 [-0.15, 0.18], 0.8479		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7082		0.7039		0.5252	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	4/83 (4.8)	5/39 (12.8)	11/148 (7.4)	11/80 (13.8)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.38 [0.11, 1.32], 0.1276		0.54 [0.25, 1.19], 0.1271	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.34 [0.09, 1.36], 0.1149		0.50 [0.21, 1.22], 0.1231	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.08 [-0.19, 0.03], 0.1712		-0.06 [-0.15, 0.02], 0.1522	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	2/21 (9.5)	2/36 (5.6)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	1.05 [0.22, 4.99], 0.9511		0.58 [0.09, 3.84], 0.5751		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	1.06 [0.19, 5.93], 0.9510		0.56 [0.07, 4.29], 0.5716		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9506		-0.04 [-0.19, 0.11], 0.5946		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.3.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.7530		0.5400		0.6992	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	9/41 (22.0)	5/83 (6.0)	0/39 (0.0)	8/148 (5.4)	9/80 (11.3)
RR [95%-CI]; p-value	0.21 [0.06, 0.73], 0.0142		4.76 [0.27, 84.97], 0.2888		0.48 [0.19, 1.20], 0.1155	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0061		5.00 [0.27, 93.86], 0.2345		0.45 [0.17, 1.22], 0.1089	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.04], 0.0129		0.05 [-0.01, 0.11], 0.1321		-0.06 [-0.14, 0.02], 0.1432	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	3/21 (14.3)	1/36 (2.8)	0/21 (0.0)	2/86 (2.3)	3/42 (7.1)
RR [95%-CI]; p-value	0.14 [0.02, 1.27], 0.0805		1.19 [0.04, 34.13], 0.9173		0.33 [0.06, 1.87], 0.2090	
OR [95%-CI]; p-value	0.12 [0.01, 1.25], 0.0405		1.20 [0.04, 37.33], 0.9171		0.31 [0.05, 1.93], 0.1866	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.03], 0.1194		0.00 [-0.08, 0.09], 0.9153		-0.05 [-0.13, 0.04], 0.2619	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_3_m_pt_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.3.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.9305		0.2249		0.2238	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	2/65 (3.1)	5/41 (12.2)	7/83 (8.4)	1/39 (2.6)	9/148 (6.1)	6/80 (7.5)
RR [95%-CI]; p-value	0.25 [0.05, 1.24], 0.0901		3.29 [0.42, 25.82], 0.2574		0.81 [0.30, 2.20], 0.6800	
OR [95%-CI]; p-value	0.23 [0.04, 1.24], 0.0656		3.50 [0.42, 29.49], 0.2219		0.80 [0.27, 2.33], 0.6800	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.0999		0.06 [-0.02, 0.14], 0.1386		-0.01 [-0.08, 0.06], 0.6885	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	3/21 (14.3)	0/36 (0.0)	1/21 (4.8)	2/86 (2.3)	4/42 (9.5)
RR [95%-CI]; p-value	0.28 [0.05, 1.56], 0.1457		0.29 [0.01, 8.22], 0.4663		0.24 [0.05, 1.28], 0.0954	
OR [95%-CI]; p-value	0.25 [0.04, 1.62], 0.1221		0.28 [0.01, 8.65], 0.4372		0.23 [0.04, 1.29], 0.0704	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2054		-0.03 [-0.13, 0.06], 0.5001		-0.07 [-0.17, 0.02], 0.1347	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_3_m_pt_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.3.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.3645		0.8928		0.3907	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	3/41 (7.3)	3/83 (3.6)	4/39 (10.3)	6/148 (4.1)	7/80 (8.8)
RR [95%-CI]; p-value	0.63 [0.13, 2.98], 0.5606		0.35 [0.08, 1.50], 0.1580		0.46 [0.16, 1.33], 0.1533	
OR [95%-CI]; p-value	0.61 [0.12, 3.19], 0.5577		0.33 [0.07, 1.54], 0.1413		0.44 [0.14, 1.36], 0.1445	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.5758		-0.07 [-0.17, 0.04], 0.2078		-0.05 [-0.12, 0.02], 0.1860	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	1/21 (4.8)	1/36 (2.8)	2/21 (9.5)	6/86 (7.0)	3/42 (7.1)
RR [95%-CI]; p-value	2.10 [0.26, 16.90], 0.4857		0.29 [0.03, 3.03], 0.3019		0.98 [0.26, 3.71], 0.9725	
OR [95%-CI]; p-value	2.22 [0.24, 20.27], 0.4689		0.27 [0.02, 3.19], 0.2712		0.98 [0.23, 4.11], 0.9725	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4052		-0.07 [-0.20, 0.07], 0.3329		-0.00 [-0.10, 0.09], 0.9726	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_3_m_pt_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.8.1.1.s4.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.4631		0.6212		0.1947	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	1/41 (2.4)	1/83 (1.2)	2/39 (5.1)	1/148 (0.7)	3/80 (3.8)
RR [95%-CI]; p-value	0.31 [0.01, 9.12], 0.4996		0.23 [0.02, 2.51], 0.2310		0.18 [0.02, 1.70], 0.1349	
OR [95%-CI]; p-value	0.31 [0.01, 9.38], 0.4752		0.23 [0.02, 2.57], 0.1919		0.17 [0.02, 1.71], 0.0915	
RD [95%-CI]; p-value	-0.02 [-0.07, 0.03], 0.5253		-0.04 [-0.11, 0.03], 0.2928		-0.03 [-0.07, 0.01], 0.1677	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	0/21 (0.0)	1/36 (2.8)	1/21 (4.8)	3/86 (3.5)	1/42 (2.4)
RR [95%-CI]; p-value	1.72 [0.08, 36.59], 0.7281		0.58 [0.04, 8.85], 0.6976		1.47 [0.16, 13.66], 0.7374	
OR [95%-CI]; p-value	1.75 [0.08, 40.48], 0.7238		0.57 [0.03, 9.64], 0.6945		1.48 [0.15, 14.69], 0.7353	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6951		-0.02 [-0.13, 0.09], 0.7130		0.01 [-0.05, 0.07], 0.7186	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_8_1_1_m_soc_sae5pct_race_pp.sas using SAS 9.4

Table 12.4.8.1.2.s4.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_8_1_2_m_pt_sae5pct_race_pp.sas using SAS 9.4

Table 12.4.5.1.1.s4.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_5_1_1_m_soc_aeg35pct_race_pp.sas using SAS 9.4

Table 12.4.5.1.2.s4.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_5_1_2_m_pt_aeg35pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4423		0.1555		0.1997	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	11/41 (26.8)	16/83 (19.3)	2/39 (5.1)	29/148 (19.6)	13/80 (16.3)
RR [95%-CI]; p-value	0.75 [0.37, 1.50], 0.4117		3.76 [0.91, 15.55], 0.0676		1.21 [0.67, 2.19], 0.5375	
OR [95%-CI]; p-value	0.68 [0.27, 1.71], 0.4132		4.42 [0.96, 20.28], 0.0399		1.26 [0.61, 2.58], 0.5341	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.10], 0.4225		0.14 [0.03, 0.25], 0.0113		0.03 [-0.07, 0.14], 0.5248	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	8/50 (16.0)	7/21 (33.3)	7/36 (19.4)	4/21 (19.0)	15/86 (17.4)	11/42 (26.2)
RR [95%-CI]; p-value	0.48 [0.20, 1.15], 0.1010		1.02 [0.34, 3.08], 0.9708		0.67 [0.34, 1.32], 0.2447	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1025		1.03 [0.26, 4.02], 0.9708		0.60 [0.25, 1.44], 0.2480	
RD [95%-CI]; p-value	-0.17 [-0.40, 0.05], 0.1324		0.00 [-0.21, 0.22], 0.9707		-0.09 [-0.24, 0.07], 0.2695	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8217		0.5654		0.5665	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	10/41 (24.4)	9/83 (10.8)	5/39 (12.8)	17/148 (11.5)	15/80 (18.8)
RR [95%-CI]; p-value	0.50 [0.22, 1.17], 0.1120		0.85 [0.30, 2.36], 0.7487		0.61 [0.32, 1.16], 0.1327	
OR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1066		0.83 [0.26, 2.65], 0.7493		0.56 [0.26, 1.20], 0.1318	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.03], 0.1236		-0.02 [-0.14, 0.10], 0.7555		-0.07 [-0.17, 0.03], 0.1536	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	5/21 (23.8)	5/36 (13.9)	2/21 (9.5)	12/86 (14.0)	7/42 (16.7)
RR [95%-CI]; p-value	0.59 [0.21, 1.64], 0.3114		1.46 [0.31, 6.86], 0.6331		0.84 [0.36, 1.97], 0.6841	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3141		1.53 [0.27, 8.70], 0.6281		0.81 [0.29, 2.24], 0.6852	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3506		0.04 [-0.13, 0.21], 0.6125		-0.03 [-0.16, 0.11], 0.6924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.6268		0.3277		0.3324	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	19/65 (29.2)	11/41 (26.8)	21/83 (25.3)	8/39 (20.5)	40/148 (27.0)	19/80 (23.8)
RR [95%-CI]; p-value	1.09 [0.58, 2.05], 0.7901		1.23 [0.60, 2.53], 0.5679		1.14 [0.71, 1.83], 0.5927	
OR [95%-CI]; p-value	1.13 [0.47, 2.70], 0.7892		1.31 [0.52, 3.30], 0.5623		1.19 [0.63, 2.23], 0.5897	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7879		0.05 [-0.11, 0.21], 0.5513		0.03 [-0.08, 0.15], 0.5848	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	12/50 (24.0)	6/21 (28.6)	7/36 (19.4)	6/21 (28.6)	19/86 (22.1)	12/42 (28.6)
RR [95%-CI]; p-value	0.84 [0.36, 1.94], 0.6831		0.68 [0.26, 1.76], 0.4264		0.77 [0.42, 1.44], 0.4173	
OR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6861		0.60 [0.17, 2.12], 0.4283		0.71 [0.31, 1.64], 0.4218	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.18], 0.6925		-0.09 [-0.32, 0.14], 0.4416		-0.06 [-0.23, 0.10], 0.4341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.6921		0.5141		0.5743	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	9/65 (13.8)	4/41 (9.8)	5/83 (6.0)	2/39 (5.1)	14/148 (9.5)	6/80 (7.5)
RR [95%-CI]; p-value	1.42 [0.47, 4.31], 0.5368		1.17 [0.24, 5.79], 0.8432		1.26 [0.50, 3.15], 0.6198	
OR [95%-CI]; p-value	1.49 [0.43, 5.18], 0.5318		1.19 [0.22, 6.40], 0.8427		1.29 [0.48, 3.49], 0.6177	
RD [95%-CI]; p-value	0.04 [-0.08, 0.16], 0.5169		0.01 [-0.08, 0.10], 0.8384		0.02 [-0.05, 0.09], 0.6063	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	1/21 (4.8)	3/36 (8.3)	0/21 (0.0)	5/86 (5.8)	1/42 (2.4)
RR [95%-CI]; p-value	0.84 [0.08, 8.77], 0.8842		3.58 [0.19, 68.18], 0.3958		2.44 [0.29, 20.24], 0.4081	
OR [95%-CI]; p-value	0.83 [0.07, 9.72], 0.8842		3.82 [0.18, 80.10], 0.3566		2.53 [0.29, 22.38], 0.3883	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.10], 0.8880		0.06 [-0.05, 0.17], 0.2866		0.03 [-0.03, 0.10], 0.3197	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.9987		0.1455		0.2915	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	5/83 (6.0)	4/39 (10.3)	12/148 (8.1)	10/80 (12.5)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.59 [0.17, 2.07], 0.4073		0.65 [0.29, 1.43], 0.2852	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.56 [0.14, 2.22], 0.4043		0.62 [0.25, 1.50], 0.2838	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.04 [-0.15, 0.07], 0.4429		-0.04 [-0.13, 0.04], 0.3099	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	1/21 (4.8)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		3.50 [0.45, 27.12], 0.2304		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		4.00 [0.45, 35.79], 0.1865		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.12 [-0.03, 0.27], 0.1249		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8524		0.7540		0.6823	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	13/41 (31.7)	14/83 (16.9)	8/39 (20.5)	27/148 (18.2)	21/80 (26.3)
RR [95%-CI]; p-value	0.63 [0.33, 1.22], 0.1724		0.82 [0.38, 1.80], 0.6234		0.69 [0.42, 1.15], 0.1548	
OR [95%-CI]; p-value	0.54 [0.22, 1.32], 0.1725		0.79 [0.30, 2.07], 0.6253		0.63 [0.33, 1.20], 0.1570	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1834		-0.04 [-0.19, 0.11], 0.6342		-0.08 [-0.19, 0.03], 0.1714	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	10/50 (20.0)	6/21 (28.6)	7/36 (19.4)	4/21 (19.0)	17/86 (19.8)	10/42 (23.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.68], 0.4240		1.02 [0.34, 3.08], 0.9708		0.83 [0.42, 1.65], 0.5963	
OR [95%-CI]; p-value	0.63 [0.19, 2.02], 0.4302		1.03 [0.26, 4.02], 0.9708		0.79 [0.32, 1.91], 0.5987	
RD [95%-CI]; p-value	-0.09 [-0.31, 0.14], 0.4508		0.00 [-0.21, 0.22], 0.9707		-0.04 [-0.19, 0.11], 0.6066	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0292		0.6230		0.2304	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	14/65 (21.5)	10/41 (24.4)	11/83 (13.3)	8/39 (20.5)	25/148 (16.9)	18/80 (22.5)
RR [95%-CI]; p-value	0.88 [0.43, 1.80], 0.7318		0.65 [0.28, 1.48], 0.3008		0.75 [0.44, 1.29], 0.2993	
OR [95%-CI]; p-value	0.85 [0.34, 2.15], 0.7326		0.59 [0.22, 1.61], 0.3024		0.70 [0.36, 1.38], 0.3016	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.14], 0.7350		-0.07 [-0.22, 0.07], 0.3305		-0.06 [-0.17, 0.05], 0.3160	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	10/21 (47.6)	9/36 (25.0)	6/21 (28.6)	15/86 (17.4)	16/42 (38.1)
RR [95%-CI]; p-value	0.25 [0.11, 0.60], 0.0020		0.88 [0.36, 2.11], 0.7666		0.46 [0.25, 0.83], 0.0107	
OR [95%-CI]; p-value	0.15 [0.04, 0.50], 0.0010		0.83 [0.25, 2.80], 0.7677		0.34 [0.15, 0.79], 0.0104	
RD [95%-CI]; p-value	-0.36 [-0.59, -0.12], 0.0026		-0.04 [-0.28, 0.20], 0.7700		-0.21 [-0.37, -0.04], 0.0156	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.0801		0.6920		0.1021	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	9/41 (22.0)	7/83 (8.4)	4/39 (10.3)	11/148 (7.4)	13/80 (16.3)
RR [95%-CI]; p-value	0.28 [0.09, 0.85], 0.0249		0.82 [0.26, 2.64], 0.7427		0.46 [0.21, 0.97], 0.0424	
OR [95%-CI]; p-value	0.23 [0.07, 0.82], 0.0157		0.81 [0.22, 2.93], 0.7431		0.41 [0.18, 0.97], 0.0384	
RD [95%-CI]; p-value	-0.16 [-0.30, -0.02], 0.0265		-0.02 [-0.13, 0.09], 0.7507		-0.09 [-0.18, 0.00], 0.0581	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	2/21 (9.5)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	1.47 [0.33, 6.50], 0.6115		1.17 [0.33, 4.18], 0.8130		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	1.55 [0.29, 8.15], 0.6049		1.20 [0.27, 5.40], 0.8120		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	0.04 [-0.11, 0.20], 0.5791		0.02 [-0.17, 0.22], 0.8089		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8592		0.7351		0.8525	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	6/41 (14.6)	7/83 (8.4)	2/39 (5.1)	15/148 (10.1)	8/80 (10.0)
RR [95%-CI]; p-value	0.84 [0.31, 2.25], 0.7301		1.64 [0.36, 7.55], 0.5225		1.01 [0.45, 2.29], 0.9742	
OR [95%-CI]; p-value	0.82 [0.26, 2.56], 0.7304		1.70 [0.34, 8.61], 0.5148		1.02 [0.41, 2.51], 0.9742	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.11], 0.7345		0.03 [-0.06, 0.12], 0.4788		0.00 [-0.08, 0.08], 0.9742	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	7/42 (16.7)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		1.17 [0.33, 4.18], 0.8130		0.91 [0.39, 2.10], 0.8201	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		1.20 [0.27, 5.40], 0.8120		0.89 [0.33, 2.43], 0.8206	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.02 [-0.17, 0.22], 0.8089		-0.02 [-0.15, 0.12], 0.8229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5320		0.8298		0.6179	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	6/41 (14.6)	8/83 (9.6)	4/39 (10.3)	11/148 (7.4)	10/80 (12.5)
RR [95%-CI]; p-value	0.32 [0.08, 1.19], 0.0889		0.94 [0.30, 2.93], 0.9148		0.59 [0.26, 1.34], 0.2096	
OR [95%-CI]; p-value	0.28 [0.07, 1.20], 0.0715		0.93 [0.26, 3.31], 0.9149		0.56 [0.23, 1.39], 0.2066	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.02], 0.1007		-0.01 [-0.12, 0.11], 0.9157		-0.05 [-0.13, 0.03], 0.2364	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	3/50 (6.0)	2/21 (9.5)	4/36 (11.1)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	0.63 [0.11, 3.50], 0.5975		1.17 [0.23, 5.84], 0.8511		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	0.61 [0.09, 3.92], 0.5964		1.19 [0.20, 7.11], 0.8506		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6261		0.02 [-0.15, 0.18], 0.8479		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7082		0.7039		0.5252	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	4/83 (4.8)	5/39 (12.8)	11/148 (7.4)	11/80 (13.8)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.38 [0.11, 1.32], 0.1276		0.54 [0.25, 1.19], 0.1271	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.34 [0.09, 1.36], 0.1149		0.50 [0.21, 1.22], 0.1231	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.08 [-0.19, 0.03], 0.1712		-0.06 [-0.15, 0.02], 0.1522	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	2/21 (9.5)	2/36 (5.6)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	1.05 [0.22, 4.99], 0.9511		0.58 [0.09, 3.84], 0.5751		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	1.06 [0.19, 5.93], 0.9510		0.56 [0.07, 4.29], 0.5716		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9506		-0.04 [-0.19, 0.11], 0.5946		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.4.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.7530		0.5400		0.6992	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	9/41 (22.0)	5/83 (6.0)	0/39 (0.0)	8/148 (5.4)	9/80 (11.3)
RR [95%-CI]; p-value	0.21 [0.06, 0.73], 0.0142		4.76 [0.27, 84.97], 0.2888		0.48 [0.19, 1.20], 0.1155	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0061		5.00 [0.27, 93.86], 0.2345		0.45 [0.17, 1.22], 0.1089	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.04], 0.0129		0.05 [-0.01, 0.11], 0.1321		-0.06 [-0.14, 0.02], 0.1432	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	3/21 (14.3)	1/36 (2.8)	0/21 (0.0)	2/86 (2.3)	3/42 (7.1)
RR [95%-CI]; p-value	0.14 [0.02, 1.27], 0.0805		1.19 [0.04, 34.13], 0.9173		0.33 [0.06, 1.87], 0.2090	
OR [95%-CI]; p-value	0.12 [0.01, 1.25], 0.0405		1.20 [0.04, 37.33], 0.9171		0.31 [0.05, 1.93], 0.1866	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.03], 0.1194		0.00 [-0.08, 0.09], 0.9153		-0.05 [-0.13, 0.04], 0.2619	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_4_m_pt_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.6952		0.0947		0.3205	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	6/65 (9.2)	1/41 (2.4)	2/83 (2.4)	4/39 (10.3)	8/148 (5.4)	5/80 (6.3)
RR [95%-CI]; p-value	3.78 [0.47, 30.31], 0.2099		0.23 [0.04, 1.23], 0.0861		0.86 [0.29, 2.56], 0.7929	
OR [95%-CI]; p-value	4.07 [0.47, 35.09], 0.1703		0.22 [0.04, 1.23], 0.0616		0.86 [0.27, 2.71], 0.7929	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1162		-0.08 [-0.18, 0.02], 0.1270		-0.01 [-0.07, 0.06], 0.7970	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	1/21 (4.8)	4/36 (11.1)	1/21 (4.8)	9/86 (10.5)	2/42 (4.8)
RR [95%-CI]; p-value	2.10 [0.26, 16.90], 0.4857		2.33 [0.28, 19.52], 0.4343		2.20 [0.50, 9.72], 0.2994	
OR [95%-CI]; p-value	2.22 [0.24, 20.27], 0.4689		2.50 [0.26, 23.99], 0.4137		2.34 [0.48, 11.34], 0.2797	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4052		0.06 [-0.07, 0.20], 0.3645		0.06 [-0.03, 0.15], 0.2208	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9074		NA		0.8197	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	0/41 (0.0)	0/83 (0.0)	0/39 (0.0)	0/148 (0.0)	0/80 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	0/21 (0.0)	0/36 (0.0)	0/21 (0.0)	1/86 (1.2)	0/42 (0.0)
RR [95%-CI]; p-value	0.86 [0.03, 24.68], 0.9298		NA		0.99 [0.03, 28.88], 0.9946	
OR [95%-CI]; p-value	0.86 [0.03, 26.55], 0.9298		NA		0.99 [0.03, 30.05], 0.9946	
RD [95%-CI]; p-value	-0.00 [-0.08, 0.07], 0.9318		NA		-0.00 [-0.04, 0.04], 0.9946	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5930		0.0947		0.3892	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	6/65 (9.2)	1/41 (2.4)	2/83 (2.4)	4/39 (10.3)	8/148 (5.4)	5/80 (6.3)
RR [95%-CI]; p-value	3.78 [0.47, 30.31], 0.2099		0.23 [0.04, 1.23], 0.0861		0.86 [0.29, 2.56], 0.7929	
OR [95%-CI]; p-value	4.07 [0.47, 35.09], 0.1703		0.22 [0.04, 1.23], 0.0616		0.86 [0.27, 2.71], 0.7929	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1162		-0.08 [-0.18, 0.02], 0.1270		-0.01 [-0.07, 0.06], 0.7970	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	4/50 (8.0)	1/21 (4.8)	4/36 (11.1)	1/21 (4.8)	8/86 (9.3)	2/42 (4.8)
RR [95%-CI]; p-value	1.68 [0.20, 14.15], 0.6333		2.33 [0.28, 19.52], 0.4343		1.95 [0.43, 8.80], 0.3832	
OR [95%-CI]; p-value	1.74 [0.18, 16.56], 0.6265		2.50 [0.26, 23.99], 0.4137		2.05 [0.42, 10.12], 0.3688	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.5910		0.06 [-0.07, 0.20], 0.3645		0.05 [-0.04, 0.13], 0.3172	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.9606		0.7242		0.7508	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	1/41 (2.4)	0/83 (0.0)	0/39 (0.0)	3/148 (2.0)	1/80 (1.3)
RR [95%-CI]; p-value	1.89 [0.20, 17.58], 0.5750		NA		1.62 [0.17, 15.34], 0.6732	
OR [95%-CI]; p-value	1.94 [0.19, 19.26], 0.5669		NA		1.63 [0.17, 15.98], 0.6697	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5394		NA		0.01 [-0.03, 0.04], 0.6473	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	0/21 (0.0)	1/36 (2.8)	0/21 (0.0)	3/86 (3.5)	0/42 (0.0)
RR [95%-CI]; p-value	1.72 [0.08, 36.59], 0.7281		1.19 [0.04, 34.13], 0.9173		2.97 [0.15, 57.87], 0.4734	
OR [95%-CI]; p-value	1.75 [0.08, 40.48], 0.7238		1.20 [0.04, 37.33], 0.9171		3.04 [0.15, 62.02], 0.4488	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6951		0.00 [-0.08, 0.09], 0.9153		0.02 [-0.03, 0.07], 0.3700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7990		0.4348		0.4533	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	5/41 (12.2)	4/83 (4.8)	3/39 (7.7)	8/148 (5.4)	8/80 (10.0)
RR [95%-CI]; p-value	0.50 [0.14, 1.77], 0.2856		0.63 [0.15, 2.66], 0.5267		0.54 [0.21, 1.39], 0.2003	
OR [95%-CI]; p-value	0.47 [0.12, 1.87], 0.2772		0.61 [0.13, 2.86], 0.5246		0.51 [0.19, 1.43], 0.1949	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3072		-0.03 [-0.12, 0.07], 0.5554		-0.05 [-0.12, 0.03], 0.2309	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	4/21 (19.0)	5/36 (13.9)	2/21 (9.5)	11/86 (12.8)	6/42 (14.3)
RR [95%-CI]; p-value	0.63 [0.20, 2.01], 0.4342		1.46 [0.31, 6.86], 0.6331		0.90 [0.36, 2.26], 0.8146	
OR [95%-CI]; p-value	0.58 [0.15, 2.31], 0.4359		1.53 [0.27, 8.70], 0.6281		0.88 [0.30, 2.57], 0.8150	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.12], 0.4686		0.04 [-0.13, 0.21], 0.6125		-0.01 [-0.14, 0.11], 0.8178	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9074		0.8247		0.9593	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	0/41 (0.0)	1/83 (1.2)	0/39 (0.0)	1/148 (0.7)	0/80 (0.0)
RR [95%-CI]; p-value	NA		0.95 [0.03, 27.78], 0.9771		1.09 [0.04, 32.08], 0.9611	
OR [95%-CI]; p-value	NA		0.95 [0.03, 28.96], 0.9771		1.09 [0.04, 32.80], 0.9611	
RD [95%-CI]; p-value	NA		-0.00 [-0.04, 0.04], 0.9773		0.00 [-0.02, 0.02], 0.9606	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	0/21 (0.0)	1/36 (2.8)	1/21 (4.8)	2/86 (2.3)	1/42 (2.4)
RR [95%-CI]; p-value	0.86 [0.03, 24.68], 0.9298		0.58 [0.04, 8.85], 0.6976		0.98 [0.09, 10.47], 0.9845	
OR [95%-CI]; p-value	0.86 [0.03, 26.55], 0.9298		0.57 [0.03, 9.64], 0.6945		0.98 [0.09, 11.08], 0.9845	
RD [95%-CI]; p-value	-0.00 [-0.08, 0.07], 0.9318		-0.02 [-0.13, 0.09], 0.7130		-0.00 [-0.06, 0.06], 0.9845	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.9645		0.5735		0.6585	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	5/41 (12.2)	4/83 (4.8)	3/39 (7.7)	8/148 (5.4)	8/80 (10.0)
RR [95%-CI]; p-value	0.50 [0.14, 1.77], 0.2856		0.63 [0.15, 2.66], 0.5267		0.54 [0.21, 1.39], 0.2003	
OR [95%-CI]; p-value	0.47 [0.12, 1.87], 0.2772		0.61 [0.13, 2.86], 0.5246		0.51 [0.19, 1.43], 0.1949	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3072		-0.03 [-0.12, 0.07], 0.5554		-0.05 [-0.12, 0.03], 0.2309	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	4/21 (19.0)	4/36 (11.1)	2/21 (9.5)	9/86 (10.5)	6/42 (14.3)
RR [95%-CI]; p-value	0.53 [0.16, 1.76], 0.2974		1.17 [0.23, 5.84], 0.8511		0.73 [0.28, 1.92], 0.5273	
OR [95%-CI]; p-value	0.47 [0.11, 1.97], 0.2957		1.19 [0.20, 7.11], 0.8506		0.70 [0.23, 2.12], 0.5280	
RD [95%-CI]; p-value	-0.09 [-0.28, 0.10], 0.3440		0.02 [-0.15, 0.18], 0.8479		-0.04 [-0.16, 0.09], 0.5460	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8582		0.9226		0.7847	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	2/65 (3.1)	0/41 (0.0)	1/83 (1.2)	0/39 (0.0)	3/148 (2.0)	0/80 (0.0)
RR [95%-CI]; p-value	2.55 [0.12, 55.26], 0.5500		0.95 [0.03, 27.78], 0.9771		3.26 [0.17, 64.35], 0.4368	
OR [95%-CI]; p-value	2.60 [0.11, 59.18], 0.5337		0.95 [0.03, 28.96], 0.9771		3.31 [0.16, 66.91], 0.4085	
RD [95%-CI]; p-value	0.02 [-0.03, 0.07], 0.4930		-0.00 [-0.04, 0.04], 0.9773		0.01 [-0.01, 0.04], 0.3330	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	0/21 (0.0)	2/36 (5.6)	1/21 (4.8)	4/86 (4.7)	1/42 (2.4)
RR [95%-CI]; p-value	1.72 [0.08, 36.59], 0.7281		1.17 [0.11, 12.10], 0.8972		1.95 [0.23, 16.94], 0.5435	
OR [95%-CI]; p-value	1.75 [0.08, 40.48], 0.7238		1.18 [0.10, 13.81], 0.8970		2.00 [0.22, 18.47], 0.5336	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6951		0.01 [-0.11, 0.13], 0.8950		0.02 [-0.04, 0.09], 0.4875	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.6.s4.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.9350		0.3618		0.4157	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	9/65 (13.8)	11/41 (26.8)	18/83 (21.7)	4/39 (10.3)	27/148 (18.2)	15/80 (18.8)
RR [95%-CI]; p-value	0.52 [0.23, 1.14], 0.1005		2.11 [0.77, 5.83], 0.1480		0.97 [0.55, 1.72], 0.9249	
OR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.0961		2.42 [0.76, 7.72], 0.1257		0.97 [0.48, 1.95], 0.9249	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.03], 0.1106		0.11 [-0.02, 0.24], 0.0851		-0.01 [-0.11, 0.10], 0.9252	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	6/21 (28.6)	5/36 (13.9)	3/21 (14.3)	12/86 (14.0)	9/42 (21.4)
RR [95%-CI]; p-value	0.49 [0.19, 1.28], 0.1470		0.97 [0.26, 3.66], 0.9668		0.65 [0.30, 1.42], 0.2820	
OR [95%-CI]; p-value	0.41 [0.12, 1.40], 0.1474		0.97 [0.21, 4.54], 0.9668		0.59 [0.23, 1.55], 0.2836	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.07], 0.1858		-0.00 [-0.19, 0.18], 0.9669		-0.07 [-0.22, 0.07], 0.3093	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_6_m_pt_adr_race_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.8862		0.9318		0.8482	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	42/58 (72.4)	27/33 (81.8)	38/65 (58.5)	17/29 (58.6)	80/123 (65.0)	44/62 (71.0)
RR [95%-CI]; p-value	0.89 [0.71, 1.11], 0.2897		1.00 [0.69, 1.44], 0.9885		0.92 [0.75, 1.13], 0.4050	
OR [95%-CI]; p-value	0.58 [0.20, 1.68], 0.3138		0.99 [0.41, 2.42], 0.9885		0.76 [0.39, 1.48], 0.4182	
RD [95%-CI]; p-value	-0.09 [-0.27, 0.08], 0.2916		-0.00 [-0.22, 0.21], 0.9885		-0.06 [-0.20, 0.08], 0.4098	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	41/57 (71.9)	23/29 (79.3)	34/54 (63.0)	20/31 (64.5)	75/111 (67.6)	43/60 (71.7)
RR [95%-CI]; p-value	0.91 [0.71, 1.16], 0.4377		0.98 [0.70, 1.36], 0.8855		0.94 [0.77, 1.16], 0.5729	
OR [95%-CI]; p-value	0.67 [0.23, 1.95], 0.4583		0.94 [0.37, 2.35], 0.8861		0.82 [0.41, 1.64], 0.5802	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.11], 0.4416		-0.02 [-0.23, 0.20], 0.8858		-0.04 [-0.18, 0.10], 0.5755	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.4828		0.6798		0.4022	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	7/33 (21.2)	5/65 (7.7)	0/29 (0.0)	12/123 (9.8)	7/62 (11.3)
RR [95%-CI]; p-value	0.57 [0.22, 1.48], 0.2479		4.54 [0.26, 80.39], 0.3024		0.86 [0.36, 2.08], 0.7452	
OR [95%-CI]; p-value	0.51 [0.16, 1.61], 0.2452		4.83 [0.26, 91.49], 0.2485		0.85 [0.32, 2.28], 0.7456	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2708		0.06 [-0.02, 0.14], 0.1407		-0.02 [-0.11, 0.08], 0.7507	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	3/29 (10.3)	8/54 (14.8)	2/31 (6.5)	14/111 (12.6)	5/60 (8.3)
RR [95%-CI]; p-value	1.02 [0.27, 3.78], 0.9793		2.30 [0.52, 10.14], 0.2726		1.51 [0.57, 4.00], 0.4032	
OR [95%-CI]; p-value	1.02 [0.24, 4.41], 0.9793		2.52 [0.50, 12.71], 0.2493		1.59 [0.54, 4.64], 0.3954	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9792		0.08 [-0.04, 0.21], 0.2013		0.04 [-0.05, 0.14], 0.3687	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.6045		0.7179		0.8453	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	3/33 (9.1)	1/65 (1.5)	2/29 (6.9)	8/123 (6.5)	5/62 (8.1)
RR [95%-CI]; p-value	1.33 [0.37, 4.79], 0.6652		0.22 [0.02, 2.36], 0.2128		0.81 [0.28, 2.36], 0.6950	
OR [95%-CI]; p-value	1.37 [0.33, 5.71], 0.6623		0.21 [0.02, 2.43], 0.1722		0.79 [0.25, 2.53], 0.6951	
RD [95%-CI]; p-value	0.03 [-0.10, 0.16], 0.6510		-0.05 [-0.15, 0.04], 0.2788		-0.02 [-0.10, 0.06], 0.7043	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	1/29 (3.4)	2/54 (3.7)	3/31 (9.7)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	2.54 [0.31, 20.77], 0.3835		0.38 [0.07, 2.17], 0.2776		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	2.69 [0.30, 24.19], 0.3596		0.36 [0.06, 2.28], 0.2599		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.2920		-0.06 [-0.18, 0.06], 0.3112		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.8774		0.3026		0.4469	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	12/58 (20.7)	6/33 (18.2)	7/65 (10.8)	2/29 (6.9)	19/123 (15.4)	8/62 (12.9)
RR [95%-CI]; p-value	1.14 [0.47, 2.75], 0.7740		1.56 [0.35, 7.06], 0.5628		1.20 [0.56, 2.58], 0.6459	
OR [95%-CI]; p-value	1.17 [0.40, 3.49], 0.7728		1.63 [0.32, 8.37], 0.5556		1.23 [0.51, 3.00], 0.6436	
RD [95%-CI]; p-value	0.03 [-0.14, 0.19], 0.7697		0.04 [-0.08, 0.16], 0.5239		0.03 [-0.08, 0.13], 0.6352	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	4/29 (13.8)	5/54 (9.3)	5/31 (16.1)	13/111 (11.7)	9/60 (15.0)
RR [95%-CI]; p-value	1.02 [0.33, 3.10], 0.9756		0.57 [0.18, 1.83], 0.3476		0.78 [0.35, 1.72], 0.5391	
OR [95%-CI]; p-value	1.02 [0.28, 3.72], 0.9756		0.53 [0.14, 2.00], 0.3440		0.75 [0.30, 1.88], 0.5399	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9755		-0.07 [-0.22, 0.08], 0.3719		-0.03 [-0.14, 0.08], 0.5520	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.6733		0.9434		0.6462	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	4/58 (6.9)	2/33 (6.1)	3/65 (4.6)	0/29 (0.0)	7/123 (5.7)	2/62 (3.2)
RR [95%-CI]; p-value	1.14 [0.22, 5.88], 0.8775		2.72 [0.14, 52.66], 0.5074		1.76 [0.38, 8.24], 0.4704	
OR [95%-CI]; p-value	1.15 [0.20, 6.63], 0.8772		2.81 [0.14, 57.86], 0.4861		1.81 [0.36, 8.99], 0.4619	
RD [95%-CI]; p-value	0.01 [-0.10, 0.11], 0.8752		0.03 [-0.04, 0.10], 0.4073		0.02 [-0.04, 0.08], 0.4213	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	1/29 (3.4)	2/54 (3.7)	0/31 (0.0)	6/111 (5.4)	1/60 (1.7)
RR [95%-CI]; p-value	2.04 [0.24, 17.39], 0.5162		2.33 [0.11, 50.15], 0.5883		3.24 [0.40, 26.32], 0.2707	
OR [95%-CI]; p-value	2.11 [0.23, 19.82], 0.5037		2.38 [0.10, 54.59], 0.5753		3.37 [0.40, 28.68], 0.2390	
RD [95%-CI]; p-value	0.04 [-0.06, 0.13], 0.4560		0.02 [-0.05, 0.09], 0.5337		0.04 [-0.02, 0.09], 0.1675	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9612		NA		0.9785	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	0/33 (0.0)	0/65 (0.0)	0/29 (0.0)	0/123 (0.0)	0/62 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	1/29 (3.4)	0/54 (0.0)	0/31 (0.0)	1/111 (0.9)	1/60 (1.7)
RR [95%-CI]; p-value	0.51 [0.03, 7.84], 0.6283		NA		0.54 [0.03, 8.49], 0.6615	
OR [95%-CI]; p-value	0.50 [0.03, 8.29], 0.6222		NA		0.54 [0.03, 8.73], 0.6567	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.06], 0.6565		NA		-0.01 [-0.04, 0.03], 0.6838	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.8199		NA		0.7700	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	1/33 (3.0)	0/65 (0.0)	0/29 (0.0)	0/123 (0.0)	1/62 (1.6)
RR [95%-CI]; p-value	0.28 [0.01, 8.18], 0.4614		NA		0.25 [0.01, 7.38], 0.4230	
OR [95%-CI]; p-value	0.28 [0.01, 8.45], 0.4313		NA		0.25 [0.01, 7.49], 0.3861	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.04], 0.4989		NA		-0.01 [-0.05, 0.02], 0.4770	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	0/57 (0.0)	0/29 (0.0)	0/54 (0.0)	0/31 (0.0)	0/111 (0.0)	0/60 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.7085		0.4265		0.3327	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	36/58 (62.1)	26/33 (78.8)	33/65 (50.8)	16/29 (55.2)	69/123 (56.1)	42/62 (67.7)
RR [95%-CI]; p-value	0.79 [0.60, 1.03], 0.0811		0.92 [0.61, 1.38], 0.6881		0.83 [0.66, 1.04], 0.1115	
OR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.0999		0.84 [0.35, 2.02], 0.6931		0.61 [0.32, 1.15], 0.1270	
RD [95%-CI]; p-value	-0.17 [-0.35, 0.02], 0.0801		-0.04 [-0.26, 0.17], 0.6922		-0.12 [-0.26, 0.03], 0.1173	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	32/57 (56.1)	19/29 (65.5)	27/54 (50.0)	13/31 (41.9)	59/111 (53.2)	32/60 (53.3)
RR [95%-CI]; p-value	0.86 [0.60, 1.22], 0.3868		1.19 [0.73, 1.95], 0.4841		1.00 [0.74, 1.34], 0.9820	
OR [95%-CI]; p-value	0.67 [0.27, 1.70], 0.4027		1.38 [0.57, 3.37], 0.4734		0.99 [0.53, 1.86], 0.9820	
RD [95%-CI]; p-value	-0.09 [-0.31, 0.12], 0.3942		0.08 [-0.14, 0.30], 0.4704		-0.00 [-0.16, 0.15], 0.9820	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.5521		0.0281		0.0645	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	21/58 (36.2)	13/33 (39.4)	22/65 (33.8)	4/29 (13.8)	43/123 (35.0)	17/62 (27.4)
RR [95%-CI]; p-value	0.92 [0.53, 1.58], 0.7611		2.45 [0.93, 6.48], 0.0701		1.27 [0.80, 2.04], 0.3123	
OR [95%-CI]; p-value	0.87 [0.36, 2.11], 0.7625		3.20 [0.99, 10.34], 0.0447		1.42 [0.73, 2.78], 0.3011	
RD [95%-CI]; p-value	-0.03 [-0.24, 0.18], 0.7635		0.20 [0.03, 0.37], 0.0210		0.08 [-0.06, 0.21], 0.2891	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	17/57 (29.8)	12/29 (41.4)	14/54 (25.9)	12/31 (38.7)	31/111 (27.9)	24/60 (40.0)
RR [95%-CI]; p-value	0.72 [0.40, 1.30], 0.2754		0.67 [0.36, 1.26], 0.2138		0.70 [0.45, 1.07], 0.1019	
OR [95%-CI]; p-value	0.60 [0.24, 1.53], 0.2839		0.55 [0.22, 1.43], 0.2182		0.58 [0.30, 1.13], 0.1068	
RD [95%-CI]; p-value	-0.12 [-0.33, 0.10], 0.2922		-0.13 [-0.34, 0.08], 0.2273		-0.12 [-0.27, 0.03], 0.1133	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.6045		0.7179		0.8453	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	3/33 (9.1)	1/65 (1.5)	2/29 (6.9)	8/123 (6.5)	5/62 (8.1)
RR [95%-CI]; p-value	1.33 [0.37, 4.79], 0.6652		0.22 [0.02, 2.36], 0.2128		0.81 [0.28, 2.36], 0.6950	
OR [95%-CI]; p-value	1.37 [0.33, 5.71], 0.6623		0.21 [0.02, 2.43], 0.1722		0.79 [0.25, 2.53], 0.6951	
RD [95%-CI]; p-value	0.03 [-0.10, 0.16], 0.6510		-0.05 [-0.15, 0.04], 0.2788		-0.02 [-0.10, 0.06], 0.7043	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	1/29 (3.4)	2/54 (3.7)	3/31 (9.7)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	2.54 [0.31, 20.77], 0.3835		0.38 [0.07, 2.17], 0.2776		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	2.69 [0.30, 24.19], 0.3596		0.36 [0.06, 2.28], 0.2599		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.2920		-0.06 [-0.18, 0.06], 0.3112		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.9039		0.4288		0.5257	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	4/58 (6.9)	5/33 (15.2)	4/65 (6.2)	2/29 (6.9)	8/123 (6.5)	7/62 (11.3)
RR [95%-CI]; p-value	0.46 [0.13, 1.58], 0.2147		0.89 [0.17, 4.60], 0.8917		0.58 [0.22, 1.52], 0.2638	
OR [95%-CI]; p-value	0.41 [0.10, 1.67], 0.2047		0.89 [0.15, 5.13], 0.8918		0.55 [0.19, 1.58], 0.2603	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2432		-0.01 [-0.12, 0.10], 0.8939		-0.05 [-0.14, 0.04], 0.2974	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	4/29 (13.8)	3/54 (5.6)	0/31 (0.0)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3127		3.50 [0.18, 67.64], 0.4070		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3065		3.65 [0.18, 75.26], 0.3717		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3495		0.04 [-0.04, 0.11], 0.3003		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.2944		0.2435		0.1577	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	13/58 (22.4)	9/33 (27.3)	15/65 (23.1)	2/29 (6.9)	28/123 (22.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.82 [0.39, 1.71], 0.6006		3.35 [0.82, 13.69], 0.0929		1.28 [0.69, 2.40], 0.4359	
OR [95%-CI]; p-value	0.77 [0.29, 2.06], 0.6027		4.05 [0.86, 19.04], 0.0598		1.37 [0.63, 2.97], 0.4292	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.14], 0.6087		0.16 [0.02, 0.30], 0.0214		0.05 [-0.07, 0.17], 0.4142	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	8/54 (14.8)	4/31 (12.9)	16/111 (14.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		1.15 [0.38, 3.50], 0.8083		0.67 [0.34, 1.29], 0.2269	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		1.17 [0.32, 4.27], 0.8075		0.61 [0.27, 1.37], 0.2278	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		0.02 [-0.13, 0.17], 0.8045		-0.07 [-0.20, 0.05], 0.2479	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.5656		0.4841		0.4231	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	9/58 (15.5)	8/33 (24.2)	9/65 (13.8)	3/29 (10.3)	18/123 (14.6)	11/62 (17.7)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3042		1.34 [0.39, 4.58], 0.6426		0.82 [0.42, 1.64], 0.5817	
OR [95%-CI]; p-value	0.57 [0.20, 1.67], 0.3046		1.39 [0.35, 5.58], 0.6385		0.79 [0.35, 1.81], 0.5831	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3240		0.04 [-0.10, 0.17], 0.6216		-0.03 [-0.14, 0.08], 0.5924	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	7/29 (24.1)	5/54 (9.3)	4/31 (12.9)	11/111 (9.9)	11/60 (18.3)
RR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.1020		0.72 [0.21, 2.48], 0.5994		0.54 [0.25, 1.17], 0.1195	
OR [95%-CI]; p-value	0.37 [0.11, 1.23], 0.0957		0.69 [0.17, 2.78], 0.5992		0.49 [0.20, 1.21], 0.1164	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1273		-0.04 [-0.18, 0.10], 0.6127		-0.08 [-0.20, 0.03], 0.1425	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.9095		0.2897		0.4332	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	16/58 (27.6)	9/33 (27.3)	18/65 (27.7)	6/29 (20.7)	34/123 (27.6)	15/62 (24.2)
RR [95%-CI]; p-value	1.01 [0.50, 2.03], 0.9743		1.34 [0.59, 3.02], 0.4826		1.14 [0.68, 1.93], 0.6190	
OR [95%-CI]; p-value	1.02 [0.39, 2.65], 0.9743		1.47 [0.51, 4.20], 0.4720		1.20 [0.59, 2.42], 0.6158	
RD [95%-CI]; p-value	0.00 [-0.19, 0.19], 0.9743		0.07 [-0.11, 0.25], 0.4538		0.03 [-0.10, 0.17], 0.6105	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	15/57 (26.3)	8/29 (27.6)	10/54 (18.5)	8/31 (25.8)	25/111 (22.5)	16/60 (26.7)
RR [95%-CI]; p-value	0.95 [0.46, 1.98], 0.8996		0.72 [0.32, 1.63], 0.4266		0.84 [0.49, 1.45], 0.5423	
OR [95%-CI]; p-value	0.94 [0.34, 2.56], 0.8999		0.65 [0.23, 1.88], 0.4286		0.80 [0.39, 1.65], 0.5447	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9003		-0.07 [-0.26, 0.11], 0.4416		-0.04 [-0.18, 0.09], 0.5510	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.8839		0.2850		0.5047	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	5/33 (15.2)	6/65 (9.2)	1/29 (3.4)	13/123 (10.6)	6/62 (9.7)
RR [95%-CI]; p-value	0.80 [0.27, 2.31], 0.6755		2.68 [0.34, 21.24], 0.3515		1.09 [0.44, 2.73], 0.8507	
OR [95%-CI]; p-value	0.77 [0.22, 2.65], 0.6761		2.85 [0.33, 24.80], 0.3240		1.10 [0.40, 3.06], 0.8504	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.12], 0.6837		0.06 [-0.04, 0.15], 0.2415		0.01 [-0.08, 0.10], 0.8485	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	5/29 (17.2)	5/54 (9.3)	4/31 (12.9)	12/111 (10.8)	9/60 (15.0)
RR [95%-CI]; p-value	0.71 [0.25, 2.05], 0.5293		0.72 [0.21, 2.48], 0.5994		0.72 [0.32, 1.61], 0.4253	
OR [95%-CI]; p-value	0.67 [0.19, 2.34], 0.5302		0.69 [0.17, 2.78], 0.5992		0.69 [0.27, 1.74], 0.4257	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5478		-0.04 [-0.18, 0.10], 0.6127		-0.04 [-0.15, 0.07], 0.4439	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5859		0.0578		0.0694	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	11/58 (19.0)	11/33 (33.3)	7/65 (10.8)	7/29 (24.1)	18/123 (14.6)	18/62 (29.0)
RR [95%-CI]; p-value	0.57 [0.28, 1.17], 0.1238		0.45 [0.17, 1.16], 0.0965		0.50 [0.28, 0.90], 0.0201	
OR [95%-CI]; p-value	0.47 [0.18, 1.24], 0.1238		0.38 [0.12, 1.21], 0.0927		0.42 [0.20, 0.88], 0.0195	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1380		-0.13 [-0.31, 0.04], 0.1299		-0.14 [-0.27, -0.01], 0.0288	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	12/57 (21.1)	8/29 (27.6)	14/54 (25.9)	5/31 (16.1)	26/111 (23.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.76 [0.35, 1.66], 0.4942		1.61 [0.64, 4.04], 0.3123		1.08 [0.60, 1.94], 0.7946	
OR [95%-CI]; p-value	0.70 [0.25, 1.97], 0.4978		1.82 [0.59, 5.66], 0.2967		1.11 [0.52, 2.35], 0.7939	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.13], 0.5094		0.10 [-0.08, 0.27], 0.2710		0.02 [-0.11, 0.15], 0.7922	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
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N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5701		0.6003		0.5455	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	12/58 (20.7)	11/33 (33.3)	10/65 (15.4)	5/29 (17.2)	22/123 (17.9)	16/62 (25.8)
RR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1803		0.89 [0.33, 2.38], 0.8198		0.69 [0.39, 1.22], 0.2051	
OR [95%-CI]; p-value	0.52 [0.20, 1.37], 0.1821		0.87 [0.27, 2.83], 0.8204		0.63 [0.30, 1.30], 0.2081	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.07], 0.1960		-0.02 [-0.18, 0.14], 0.8234		-0.08 [-0.21, 0.05], 0.2262	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	10/54 (18.5)	9/31 (29.0)	18/111 (16.2)	18/60 (30.0)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		0.64 [0.29, 1.40], 0.2615		0.54 [0.30, 0.96], 0.0353	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		0.56 [0.20, 1.57], 0.2627		0.45 [0.21, 0.95], 0.0349	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		-0.11 [-0.30, 0.09], 0.2792		-0.14 [-0.27, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8883		0.0491		0.1376	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	6/33 (18.2)	9/65 (13.8)	1/29 (3.4)	15/123 (12.2)	7/62 (11.3)
RR [95%-CI]; p-value	0.57 [0.20, 1.62], 0.2915		4.02 [0.53, 30.24], 0.1772		1.08 [0.46, 2.51], 0.8579	
OR [95%-CI]; p-value	0.52 [0.15, 1.76], 0.2881		4.50 [0.54, 37.31], 0.1310		1.09 [0.42, 2.83], 0.8576	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3159		0.10 [-0.00, 0.21], 0.0570		0.01 [-0.09, 0.11], 0.8560	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	5/29 (17.2)	4/54 (7.4)	6/31 (19.4)	9/111 (8.1)	11/60 (18.3)
RR [95%-CI]; p-value	0.51 [0.16, 1.62], 0.2520		0.38 [0.12, 1.25], 0.1123		0.44 [0.19, 1.01], 0.0520	
OR [95%-CI]; p-value	0.46 [0.12, 1.75], 0.2467		0.33 [0.09, 1.29], 0.0998		0.39 [0.15, 1.01], 0.0471	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2869		-0.12 [-0.28, 0.04], 0.1324		-0.10 [-0.21, 0.01], 0.0692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3444		0.4873		0.2986	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	4/33 (12.1)	3/65 (4.6)	2/29 (6.9)	4/123 (3.3)	6/62 (9.7)
RR [95%-CI]; p-value	0.14 [0.02, 1.22], 0.0753		0.67 [0.12, 3.79], 0.6500		0.34 [0.10, 1.15], 0.0817	
OR [95%-CI]; p-value	0.13 [0.01, 1.19], 0.0364		0.65 [0.10, 4.14], 0.6490		0.31 [0.09, 1.16], 0.0681	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0797		-0.02 [-0.13, 0.08], 0.6714		-0.06 [-0.14, 0.02], 0.1154	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	3/29 (10.3)	2/54 (3.7)	0/31 (0.0)	5/111 (4.5)	3/60 (5.0)
RR [95%-CI]; p-value	0.51 [0.11, 2.37], 0.3887		2.33 [0.11, 50.15], 0.5883		0.90 [0.22, 3.64], 0.8836	
OR [95%-CI]; p-value	0.48 [0.09, 2.55], 0.3818		2.38 [0.10, 54.59], 0.5753		0.90 [0.21, 3.89], 0.8836	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4259		0.02 [-0.05, 0.09], 0.5337		-0.00 [-0.07, 0.06], 0.8853	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5765		0.3627		0.8559	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	6/33 (18.2)	11/65 (16.9)	3/29 (10.3)	18/123 (14.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.66 [0.24, 1.81], 0.4234		1.64 [0.49, 5.43], 0.4212		1.01 [0.48, 2.11], 0.9829	
OR [95%-CI]; p-value	0.62 [0.19, 2.02], 0.4230		1.77 [0.45, 6.88], 0.4080		1.01 [0.42, 2.40], 0.9829	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4426		0.07 [-0.08, 0.21], 0.3690		0.00 [-0.11, 0.11], 0.9829	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	4/29 (13.8)	2/54 (3.7)	2/31 (6.5)	10/111 (9.0)	6/60 (10.0)
RR [95%-CI]; p-value	1.02 [0.33, 3.10], 0.9756		0.57 [0.09, 3.88], 0.5689		0.90 [0.34, 2.36], 0.8317	
OR [95%-CI]; p-value	1.02 [0.28, 3.72], 0.9756		0.56 [0.07, 4.17], 0.5647		0.89 [0.31, 2.58], 0.8318	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9755		-0.03 [-0.13, 0.07], 0.5905		-0.01 [-0.10, 0.08], 0.8341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5878		0.6564		0.9938	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	2/58 (3.4)	4/33 (12.1)	6/65 (9.2)	2/29 (6.9)	8/123 (6.5)	6/62 (9.7)
RR [95%-CI]; p-value	0.28 [0.06, 1.47], 0.1336		1.34 [0.29, 6.24], 0.7105		0.67 [0.24, 1.85], 0.4422	
OR [95%-CI]; p-value	0.26 [0.04, 1.50], 0.1090		1.37 [0.26, 7.25], 0.7080		0.65 [0.21, 1.96], 0.4411	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1596		0.02 [-0.09, 0.14], 0.6933		-0.03 [-0.12, 0.05], 0.4671	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	4/29 (13.8)	6/54 (11.1)	4/31 (12.9)	10/111 (9.0)	8/60 (13.3)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3127		0.86 [0.26, 2.82], 0.8047		0.68 [0.28, 1.62], 0.3799	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3065		0.84 [0.22, 3.26], 0.8050		0.64 [0.24, 1.73], 0.3792	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3495		-0.02 [-0.16, 0.13], 0.8083		-0.04 [-0.14, 0.06], 0.4022	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.4040		0.8901		0.4786	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	5/58 (8.6)	5/33 (15.2)	4/65 (6.2)	4/29 (13.8)	9/123 (7.3)	9/62 (14.5)
RR [95%-CI]; p-value	0.57 [0.18, 1.82], 0.3422		0.45 [0.12, 1.66], 0.2290		0.50 [0.21, 1.21], 0.1236	
OR [95%-CI]; p-value	0.53 [0.14, 1.98], 0.3382		0.41 [0.09, 1.77], 0.2202		0.46 [0.17, 1.24], 0.1189	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.08], 0.3676		-0.08 [-0.21, 0.06], 0.2794		-0.07 [-0.17, 0.03], 0.1542	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	3/29 (10.3)	2/54 (3.7)	3/31 (9.7)	9/111 (8.1)	6/60 (10.0)
RR [95%-CI]; p-value	1.19 [0.33, 4.25], 0.7922		0.38 [0.07, 2.17], 0.2776		0.81 [0.30, 2.17], 0.6762	
OR [95%-CI]; p-value	1.21 [0.29, 5.09], 0.7912		0.36 [0.06, 2.28], 0.2599		0.79 [0.27, 2.35], 0.6764	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7861		-0.06 [-0.18, 0.06], 0.3112		-0.02 [-0.11, 0.07], 0.6847	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8169		0.5475		0.2323	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	4/33 (12.1)	5/65 (7.7)	0/29 (0.0)	6/123 (4.9)	4/62 (6.5)
RR [95%-CI]; p-value	0.14 [0.02, 1.22], 0.0753		4.54 [0.26, 80.39], 0.3024		0.76 [0.22, 2.58], 0.6554	
OR [95%-CI]; p-value	0.13 [0.01, 1.19], 0.0364		4.83 [0.26, 91.49], 0.2485		0.74 [0.20, 2.74], 0.6550	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0797		0.06 [-0.02, 0.14], 0.1407		-0.02 [-0.09, 0.06], 0.6685	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	8/29 (27.6)	1/54 (1.9)	0/31 (0.0)	4/111 (3.6)	8/60 (13.3)
RR [95%-CI]; p-value	0.19 [0.05, 0.67], 0.0094		1.17 [0.04, 33.80], 0.9285		0.27 [0.08, 0.86], 0.0269	
OR [95%-CI]; p-value	0.15 [0.04, 0.60], 0.0034		1.17 [0.04, 35.89], 0.9284		0.24 [0.07, 0.84], 0.0174	
RD [95%-CI]; p-value	-0.22 [-0.40, -0.05], 0.0113		0.00 [-0.05, 0.06], 0.9269		-0.10 [-0.19, -0.00], 0.0398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_3_m_pt_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2599		0.4048		0.7658	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	5/33 (15.2)	4/65 (6.2)	0/29 (0.0)	5/123 (4.1)	5/62 (8.1)
RR [95%-CI]; p-value	0.11 [0.01, 0.93], 0.0429		3.63 [0.20, 66.49], 0.3847		0.50 [0.15, 1.68], 0.2637	
OR [95%-CI]; p-value	0.10 [0.01, 0.88], 0.0131		3.80 [0.19, 74.36], 0.3456		0.48 [0.13, 1.74], 0.2561	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.01], 0.0380		0.04 [-0.03, 0.12], 0.2421		-0.04 [-0.12, 0.04], 0.3038	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	3/29 (10.3)	3/54 (5.6)	2/31 (6.5)	6/111 (5.4)	5/60 (8.3)
RR [95%-CI]; p-value	0.51 [0.11, 2.37], 0.3887		0.86 [0.15, 4.88], 0.8658		0.65 [0.21, 2.04], 0.4585	
OR [95%-CI]; p-value	0.48 [0.09, 2.55], 0.3818		0.85 [0.13, 5.40], 0.8658		0.63 [0.18, 2.15], 0.4564	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4259		-0.01 [-0.11, 0.10], 0.8683		-0.03 [-0.11, 0.05], 0.4819	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_3_m_pt_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.7390		0.4617		0.3352	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	2/33 (6.1)	2/65 (3.1)	4/29 (13.8)	5/123 (4.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.85 [0.15, 4.85], 0.8581		0.22 [0.04, 1.15], 0.0730		0.42 [0.13, 1.32], 0.1383	
OR [95%-CI]; p-value	0.85 [0.13, 5.34], 0.8581		0.20 [0.03, 1.15], 0.0496		0.40 [0.12, 1.35], 0.1276	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8609		-0.11 [-0.24, 0.03], 0.1125		-0.06 [-0.14, 0.03], 0.1768	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	2/29 (6.9)	2/54 (3.7)	2/31 (6.5)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	1.27 [0.26, 6.16], 0.7651		0.57 [0.09, 3.88], 0.5689		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	1.30 [0.24, 7.14], 0.7637		0.56 [0.07, 4.17], 0.5647		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7552		-0.03 [-0.13, 0.07], 0.5905		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_3_m_pt_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.8.1.1.s5.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.7111		0.8109		0.4960	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	0/33 (0.0)	1/65 (1.5)	1/29 (3.4)	2/123 (1.6)	1/62 (1.6)
RR [95%-CI]; p-value	1.16 [0.04, 33.52], 0.9331		0.45 [0.03, 6.89], 0.5633		1.01 [0.09, 10.90], 0.9947	
OR [95%-CI]; p-value	1.16 [0.04, 35.46], 0.9330		0.44 [0.03, 7.25], 0.5534		1.01 [0.09, 11.34], 0.9947	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9317		-0.02 [-0.09, 0.05], 0.6073		0.00 [-0.04, 0.04], 0.9947	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	1/29 (3.4)	1/54 (1.9)	2/31 (6.5)	2/111 (1.8)	3/60 (5.0)
RR [95%-CI]; p-value	0.51 [0.03, 7.84], 0.6283		0.29 [0.03, 3.04], 0.2998		0.36 [0.06, 2.10], 0.2561	
OR [95%-CI]; p-value	0.50 [0.03, 8.29], 0.6222		0.27 [0.02, 3.15], 0.2686		0.35 [0.06, 2.15], 0.2361	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.06], 0.6565		-0.05 [-0.14, 0.05], 0.3358		-0.03 [-0.09, 0.03], 0.2997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_8_1_1_m_soc_sae5pct_ckd_pp.sas using SAS 9.4

Table 12.4.8.1.2.s5.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_8_1_2_m_pt_sae5pct_ckd_pp.sas using SAS 9.4

Table 12.4.5.1.1.s5.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_5_1_1_m_soc_aeg35pct_ckd_pp.sas using SAS 9.4

Table 12.4.5.1.2.s5.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_5_1_2_m_pt_aeg35pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.2944		0.2435		0.1577	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	13/58 (22.4)	9/33 (27.3)	15/65 (23.1)	2/29 (6.9)	28/123 (22.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.82 [0.39, 1.71], 0.6006		3.35 [0.82, 13.69], 0.0929		1.28 [0.69, 2.40], 0.4359	
OR [95%-CI]; p-value	0.77 [0.29, 2.06], 0.6027		4.05 [0.86, 19.04], 0.0598		1.37 [0.63, 2.97], 0.4292	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.14], 0.6087		0.16 [0.02, 0.30], 0.0214		0.05 [-0.07, 0.17], 0.4142	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	8/54 (14.8)	4/31 (12.9)	16/111 (14.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		1.15 [0.38, 3.50], 0.8083		0.67 [0.34, 1.29], 0.2269	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		1.17 [0.32, 4.27], 0.8075		0.61 [0.27, 1.37], 0.2278	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		0.02 [-0.13, 0.17], 0.8045		-0.07 [-0.20, 0.05], 0.2479	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.5656		0.4841		0.4231	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	9/58 (15.5)	8/33 (24.2)	9/65 (13.8)	3/29 (10.3)	18/123 (14.6)	11/62 (17.7)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3042		1.34 [0.39, 4.58], 0.6426		0.82 [0.42, 1.64], 0.5817	
OR [95%-CI]; p-value	0.57 [0.20, 1.67], 0.3046		1.39 [0.35, 5.58], 0.6385		0.79 [0.35, 1.81], 0.5831	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3240		0.04 [-0.10, 0.17], 0.6216		-0.03 [-0.14, 0.08], 0.5924	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	7/29 (24.1)	5/54 (9.3)	4/31 (12.9)	11/111 (9.9)	11/60 (18.3)
RR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.1020		0.72 [0.21, 2.48], 0.5994		0.54 [0.25, 1.17], 0.1195	
OR [95%-CI]; p-value	0.37 [0.11, 1.23], 0.0957		0.69 [0.17, 2.78], 0.5992		0.49 [0.20, 1.21], 0.1164	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1273		-0.04 [-0.18, 0.10], 0.6127		-0.08 [-0.20, 0.03], 0.1425	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.9095		0.2897		0.4332	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	16/58 (27.6)	9/33 (27.3)	18/65 (27.7)	6/29 (20.7)	34/123 (27.6)	15/62 (24.2)
RR [95%-CI]; p-value	1.01 [0.50, 2.03], 0.9743		1.34 [0.59, 3.02], 0.4826		1.14 [0.68, 1.93], 0.6190	
OR [95%-CI]; p-value	1.02 [0.39, 2.65], 0.9743		1.47 [0.51, 4.20], 0.4720		1.20 [0.59, 2.42], 0.6158	
RD [95%-CI]; p-value	0.00 [-0.19, 0.19], 0.9743		0.07 [-0.11, 0.25], 0.4538		0.03 [-0.10, 0.17], 0.6105	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	15/57 (26.3)	8/29 (27.6)	10/54 (18.5)	8/31 (25.8)	25/111 (22.5)	16/60 (26.7)
RR [95%-CI]; p-value	0.95 [0.46, 1.98], 0.8996		0.72 [0.32, 1.63], 0.4266		0.84 [0.49, 1.45], 0.5423	
OR [95%-CI]; p-value	0.94 [0.34, 2.56], 0.8999		0.65 [0.23, 1.88], 0.4286		0.80 [0.39, 1.65], 0.5447	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9003		-0.07 [-0.26, 0.11], 0.4416		-0.04 [-0.18, 0.09], 0.5510	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.6500		0.8707		0.5916	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	5/58 (8.6)	3/33 (9.1)	4/65 (6.2)	1/29 (3.4)	9/123 (7.3)	4/62 (6.5)
RR [95%-CI]; p-value	0.95 [0.24, 3.72], 0.9393		1.78 [0.21, 15.28], 0.5970		1.13 [0.36, 3.54], 0.8283	
OR [95%-CI]; p-value	0.94 [0.21, 4.23], 0.9393		1.84 [0.20, 17.19], 0.5893		1.14 [0.34, 3.88], 0.8279	
RD [95%-CI]; p-value	-0.00 [-0.13, 0.12], 0.9397		0.03 [-0.06, 0.12], 0.5488		0.01 [-0.07, 0.09], 0.8246	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	2/29 (6.9)	4/54 (7.4)	1/31 (3.2)	10/111 (9.0)	3/60 (5.0)
RR [95%-CI]; p-value	1.53 [0.33, 7.10], 0.5896		2.30 [0.27, 19.64], 0.4478		1.80 [0.52, 6.30], 0.3564	
OR [95%-CI]; p-value	1.59 [0.30, 8.41], 0.5838		2.40 [0.26, 22.49], 0.4303		1.88 [0.50, 7.12], 0.3452	
RD [95%-CI]; p-value	0.04 [-0.09, 0.16], 0.5594		0.04 [-0.05, 0.14], 0.3809		0.04 [-0.04, 0.12], 0.3054	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.8839		0.2850		0.5047	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	5/33 (15.2)	6/65 (9.2)	1/29 (3.4)	13/123 (10.6)	6/62 (9.7)
RR [95%-CI]; p-value	0.80 [0.27, 2.31], 0.6755		2.68 [0.34, 21.24], 0.3515		1.09 [0.44, 2.73], 0.8507	
OR [95%-CI]; p-value	0.77 [0.22, 2.65], 0.6761		2.85 [0.33, 24.80], 0.3240		1.10 [0.40, 3.06], 0.8504	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.12], 0.6837		0.06 [-0.04, 0.15], 0.2415		0.01 [-0.08, 0.10], 0.8485	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	5/29 (17.2)	5/54 (9.3)	4/31 (12.9)	12/111 (10.8)	9/60 (15.0)
RR [95%-CI]; p-value	0.71 [0.25, 2.05], 0.5293		0.72 [0.21, 2.48], 0.5994		0.72 [0.32, 1.61], 0.4253	
OR [95%-CI]; p-value	0.67 [0.19, 2.34], 0.5302		0.69 [0.17, 2.78], 0.5992		0.69 [0.27, 1.74], 0.4257	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5478		-0.04 [-0.18, 0.10], 0.6127		-0.04 [-0.15, 0.07], 0.4439	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5859		0.0578		0.0694	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	11/58 (19.0)	11/33 (33.3)	7/65 (10.8)	7/29 (24.1)	18/123 (14.6)	18/62 (29.0)
RR [95%-CI]; p-value	0.57 [0.28, 1.17], 0.1238		0.45 [0.17, 1.16], 0.0965		0.50 [0.28, 0.90], 0.0201	
OR [95%-CI]; p-value	0.47 [0.18, 1.24], 0.1238		0.38 [0.12, 1.21], 0.0927		0.42 [0.20, 0.88], 0.0195	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1380		-0.13 [-0.31, 0.04], 0.1299		-0.14 [-0.27, -0.01], 0.0288	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	12/57 (21.1)	8/29 (27.6)	14/54 (25.9)	5/31 (16.1)	26/111 (23.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.76 [0.35, 1.66], 0.4942		1.61 [0.64, 4.04], 0.3123		1.08 [0.60, 1.94], 0.7946	
OR [95%-CI]; p-value	0.70 [0.25, 1.97], 0.4978		1.82 [0.59, 5.66], 0.2967		1.11 [0.52, 2.35], 0.7939	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.13], 0.5094		0.10 [-0.08, 0.27], 0.2710		0.02 [-0.11, 0.15], 0.7922	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5701		0.6003		0.5455	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	12/58 (20.7)	11/33 (33.3)	10/65 (15.4)	5/29 (17.2)	22/123 (17.9)	16/62 (25.8)
RR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1803		0.89 [0.33, 2.38], 0.8198		0.69 [0.39, 1.22], 0.2051	
OR [95%-CI]; p-value	0.52 [0.20, 1.37], 0.1821		0.87 [0.27, 2.83], 0.8204		0.63 [0.30, 1.30], 0.2081	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.07], 0.1960		-0.02 [-0.18, 0.14], 0.8234		-0.08 [-0.21, 0.05], 0.2262	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	10/54 (18.5)	9/31 (29.0)	18/111 (16.2)	18/60 (30.0)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		0.64 [0.29, 1.40], 0.2615		0.54 [0.30, 0.96], 0.0353	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		0.56 [0.20, 1.57], 0.2627		0.45 [0.21, 0.95], 0.0349	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		-0.11 [-0.30, 0.09], 0.2792		-0.14 [-0.27, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8883		0.0491		0.1376	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	6/33 (18.2)	9/65 (13.8)	1/29 (3.4)	15/123 (12.2)	7/62 (11.3)
RR [95%-CI]; p-value	0.57 [0.20, 1.62], 0.2915		4.02 [0.53, 30.24], 0.1772		1.08 [0.46, 2.51], 0.8579	
OR [95%-CI]; p-value	0.52 [0.15, 1.76], 0.2881		4.50 [0.54, 37.31], 0.1310		1.09 [0.42, 2.83], 0.8576	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3159		0.10 [-0.00, 0.21], 0.0570		0.01 [-0.09, 0.11], 0.8560	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	5/29 (17.2)	4/54 (7.4)	6/31 (19.4)	9/111 (8.1)	11/60 (18.3)
RR [95%-CI]; p-value	0.51 [0.16, 1.62], 0.2520		0.38 [0.12, 1.25], 0.1123		0.44 [0.19, 1.01], 0.0520	
OR [95%-CI]; p-value	0.46 [0.12, 1.75], 0.2467		0.33 [0.09, 1.29], 0.0998		0.39 [0.15, 1.01], 0.0471	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2869		-0.12 [-0.28, 0.04], 0.1324		-0.10 [-0.21, 0.01], 0.0692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5765		0.3627		0.8559	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	6/33 (18.2)	11/65 (16.9)	3/29 (10.3)	18/123 (14.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.66 [0.24, 1.81], 0.4234		1.64 [0.49, 5.43], 0.4212		1.01 [0.48, 2.11], 0.9829	
OR [95%-CI]; p-value	0.62 [0.19, 2.02], 0.4230		1.77 [0.45, 6.88], 0.4080		1.01 [0.42, 2.40], 0.9829	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4426		0.07 [-0.08, 0.21], 0.3690		0.00 [-0.11, 0.11], 0.9829	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	4/29 (13.8)	2/54 (3.7)	2/31 (6.5)	10/111 (9.0)	6/60 (10.0)
RR [95%-CI]; p-value	1.02 [0.33, 3.10], 0.9756		0.57 [0.09, 3.88], 0.5689		0.90 [0.34, 2.36], 0.8317	
OR [95%-CI]; p-value	1.02 [0.28, 3.72], 0.9756		0.56 [0.07, 4.17], 0.5647		0.89 [0.31, 2.58], 0.8318	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9755		-0.03 [-0.13, 0.07], 0.5905		-0.01 [-0.10, 0.08], 0.8341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5878		0.6564		0.9938	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	2/58 (3.4)	4/33 (12.1)	6/65 (9.2)	2/29 (6.9)	8/123 (6.5)	6/62 (9.7)
RR [95%-CI]; p-value	0.28 [0.06, 1.47], 0.1336		1.34 [0.29, 6.24], 0.7105		0.67 [0.24, 1.85], 0.4422	
OR [95%-CI]; p-value	0.26 [0.04, 1.50], 0.1090		1.37 [0.26, 7.25], 0.7080		0.65 [0.21, 1.96], 0.4411	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1596		0.02 [-0.09, 0.14], 0.6933		-0.03 [-0.12, 0.05], 0.4671	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	4/29 (13.8)	6/54 (11.1)	4/31 (12.9)	10/111 (9.0)	8/60 (13.3)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3127		0.86 [0.26, 2.82], 0.8047		0.68 [0.28, 1.62], 0.3799	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3065		0.84 [0.22, 3.26], 0.8050		0.64 [0.24, 1.73], 0.3792	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3495		-0.02 [-0.16, 0.13], 0.8083		-0.04 [-0.14, 0.06], 0.4022	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.4040		0.8901		0.4786	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	5/58 (8.6)	5/33 (15.2)	4/65 (6.2)	4/29 (13.8)	9/123 (7.3)	9/62 (14.5)
RR [95%-CI]; p-value	0.57 [0.18, 1.82], 0.3422		0.45 [0.12, 1.66], 0.2290		0.50 [0.21, 1.21], 0.1236	
OR [95%-CI]; p-value	0.53 [0.14, 1.98], 0.3382		0.41 [0.09, 1.77], 0.2202		0.46 [0.17, 1.24], 0.1189	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.08], 0.3676		-0.08 [-0.21, 0.06], 0.2794		-0.07 [-0.17, 0.03], 0.1542	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	3/29 (10.3)	2/54 (3.7)	3/31 (9.7)	9/111 (8.1)	6/60 (10.0)
RR [95%-CI]; p-value	1.19 [0.33, 4.25], 0.7922		0.38 [0.07, 2.17], 0.2776		0.81 [0.30, 2.17], 0.6762	
OR [95%-CI]; p-value	1.21 [0.29, 5.09], 0.7912		0.36 [0.06, 2.28], 0.2599		0.79 [0.27, 2.35], 0.6764	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7861		-0.06 [-0.18, 0.06], 0.3112		-0.02 [-0.11, 0.07], 0.6847	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.4.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8169		0.5475		0.2323	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	4/33 (12.1)	5/65 (7.7)	0/29 (0.0)	6/123 (4.9)	4/62 (6.5)
RR [95%-CI]; p-value	0.14 [0.02, 1.22], 0.0753		4.54 [0.26, 80.39], 0.3024		0.76 [0.22, 2.58], 0.6554	
OR [95%-CI]; p-value	0.13 [0.01, 1.19], 0.0364		4.83 [0.26, 91.49], 0.2485		0.74 [0.20, 2.74], 0.6550	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0797		0.06 [-0.02, 0.14], 0.1407		-0.02 [-0.09, 0.06], 0.6685	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	8/29 (27.6)	1/54 (1.9)	0/31 (0.0)	4/111 (3.6)	8/60 (13.3)
RR [95%-CI]; p-value	0.19 [0.05, 0.67], 0.0094		1.17 [0.04, 33.80], 0.9285		0.27 [0.08, 0.86], 0.0269	
OR [95%-CI]; p-value	0.15 [0.04, 0.60], 0.0034		1.17 [0.04, 35.89], 0.9284		0.24 [0.07, 0.84], 0.0174	
RD [95%-CI]; p-value	-0.22 [-0.40, -0.05], 0.0113		0.00 [-0.05, 0.06], 0.9269		-0.10 [-0.19, -0.00], 0.0398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_4_m_pt_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.1790		0.7489		0.4668	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	2/33 (6.1)	2/65 (3.1)	1/29 (3.4)	5/123 (4.1)	3/62 (4.8)
RR [95%-CI]; p-value	0.85 [0.15, 4.85], 0.8581		0.89 [0.08, 9.45], 0.9246		0.84 [0.21, 3.40], 0.8071	
OR [95%-CI]; p-value	0.85 [0.13, 5.34], 0.8581		0.89 [0.08, 10.21], 0.9246		0.83 [0.19, 3.61], 0.8071	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8609		-0.00 [-0.08, 0.07], 0.9262		-0.01 [-0.07, 0.06], 0.8121	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	0/29 (0.0)	4/54 (7.4)	4/31 (12.9)	12/111 (10.8)	4/60 (6.7)
RR [95%-CI]; p-value	8.28 [0.49, 139.25], 0.1421		0.57 [0.15, 2.14], 0.4076		1.62 [0.55, 4.81], 0.3834	
OR [95%-CI]; p-value	9.47 [0.52, 171.03], 0.0676		0.54 [0.13, 2.33], 0.4036		1.70 [0.52, 5.51], 0.3745	
RD [95%-CI]; p-value	0.12 [0.02, 0.22], 0.0172		-0.05 [-0.19, 0.08], 0.4322		0.04 [-0.04, 0.13], 0.3425	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8217		NA		0.7710	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	0/33 (0.0)	0/65 (0.0)	0/29 (0.0)	0/123 (0.0)	0/62 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	0/29 (0.0)	0/54 (0.0)	0/31 (0.0)	1/111 (0.9)	0/60 (0.0)
RR [95%-CI]; p-value	1.04 [0.04, 29.96], 0.9840		NA		1.09 [0.04, 32.03], 0.9601	
OR [95%-CI]; p-value	1.04 [0.03, 31.80], 0.9840		NA		1.09 [0.04, 32.99], 0.9601	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9839		NA		0.00 [-0.03, 0.03], 0.9596	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2073		0.7489		0.5297	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	2/33 (6.1)	2/65 (3.1)	1/29 (3.4)	5/123 (4.1)	3/62 (4.8)
RR [95%-CI]; p-value	0.85 [0.15, 4.85], 0.8581		0.89 [0.08, 9.45], 0.9246		0.84 [0.21, 3.40], 0.8071	
OR [95%-CI]; p-value	0.85 [0.13, 5.34], 0.8581		0.89 [0.08, 10.21], 0.9246		0.83 [0.19, 3.61], 0.8071	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8609		-0.00 [-0.08, 0.07], 0.9262		-0.01 [-0.07, 0.06], 0.8121	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	0/29 (0.0)	4/54 (7.4)	4/31 (12.9)	11/111 (9.9)	4/60 (6.7)
RR [95%-CI]; p-value	7.25 [0.43, 123.33], 0.1709		0.57 [0.15, 2.14], 0.4076		1.49 [0.49, 4.47], 0.4802	
OR [95%-CI]; p-value	8.12 [0.44, 148.36], 0.0972		0.54 [0.13, 2.33], 0.4036		1.54 [0.47, 5.06], 0.4743	
RD [95%-CI]; p-value	0.11 [0.01, 0.20], 0.0326		-0.05 [-0.19, 0.08], 0.4322		0.03 [-0.05, 0.12], 0.4498	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.6034		0.8636		0.6851	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	2/58 (3.4)	1/33 (3.0)	1/65 (1.5)	0/29 (0.0)	3/123 (2.4)	1/62 (1.6)
RR [95%-CI]; p-value	1.14 [0.11, 12.08], 0.9146		0.91 [0.03, 26.31], 0.9550		1.51 [0.16, 14.24], 0.7178	
OR [95%-CI]; p-value	1.14 [0.10, 13.10], 0.9145		0.91 [0.03, 27.79], 0.9550		1.53 [0.16, 14.97], 0.7154	
RD [95%-CI]; p-value	0.00 [-0.07, 0.08], 0.9130		-0.00 [-0.06, 0.05], 0.9558		0.01 [-0.03, 0.05], 0.6968	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	0/29 (0.0)	0/54 (0.0)	0/31 (0.0)	3/111 (2.7)	0/60 (0.0)
RR [95%-CI]; p-value	3.11 [0.16, 59.97], 0.4532		NA		3.27 [0.17, 64.22], 0.4354	
OR [95%-CI]; p-value	3.22 [0.16, 66.54], 0.4246		NA		3.33 [0.16, 67.66], 0.4063	
RD [95%-CI]; p-value	0.04 [-0.04, 0.11], 0.3470		NA		0.02 [-0.02, 0.06], 0.3309	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.4529		0.9744		0.5376	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	7/33 (21.2)	6/65 (9.2)	3/29 (10.3)	12/123 (9.8)	10/62 (16.1)
RR [95%-CI]; p-value	0.49 [0.18, 1.33], 0.1606		0.89 [0.24, 3.32], 0.8651		0.60 [0.28, 1.32], 0.2075	
OR [95%-CI]; p-value	0.43 [0.13, 1.41], 0.1544		0.88 [0.20, 3.80], 0.8654		0.56 [0.23, 1.38], 0.2062	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.05], 0.1831		-0.01 [-0.14, 0.12], 0.8679		-0.06 [-0.17, 0.04], 0.2365	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	2/29 (6.9)	3/54 (5.6)	2/31 (6.5)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	1.02 [0.20, 5.23], 0.9834		0.86 [0.15, 4.88], 0.8658		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	1.02 [0.18, 5.92], 0.9834		0.85 [0.13, 5.40], 0.8658		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.00 [-0.11, 0.11], 0.9833		-0.01 [-0.11, 0.10], 0.8683		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8217		0.6641		0.4876	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	0/33 (0.0)	1/65 (1.5)	1/29 (3.4)	1/123 (0.8)	1/62 (1.6)
RR [95%-CI]; p-value	NA		0.45 [0.03, 6.89], 0.5633		0.50 [0.03, 7.92], 0.6260	
OR [95%-CI]; p-value	NA		0.44 [0.03, 7.25], 0.5534		0.50 [0.03, 8.13], 0.6195	
RD [95%-CI]; p-value	NA		-0.02 [-0.09, 0.05], 0.6073		-0.01 [-0.04, 0.03], 0.6555	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	0/29 (0.0)	1/54 (1.9)	0/31 (0.0)	2/111 (1.8)	0/60 (0.0)
RR [95%-CI]; p-value	1.04 [0.04, 29.96], 0.9840		1.17 [0.04, 33.80], 0.9285		2.18 [0.10, 47.58], 0.6203	
OR [95%-CI]; p-value	1.04 [0.03, 31.80], 0.9840		1.17 [0.04, 35.89], 0.9284		2.20 [0.10, 49.61], 0.6106	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9839		0.00 [-0.05, 0.06], 0.9269		0.01 [-0.02, 0.04], 0.5700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.6611		0.7093		0.8848	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	7/33 (21.2)	6/65 (9.2)	3/29 (10.3)	12/123 (9.8)	10/62 (16.1)
RR [95%-CI]; p-value	0.49 [0.18, 1.33], 0.1606		0.89 [0.24, 3.32], 0.8651		0.60 [0.28, 1.32], 0.2075	
OR [95%-CI]; p-value	0.43 [0.13, 1.41], 0.1544		0.88 [0.20, 3.80], 0.8654		0.56 [0.23, 1.38], 0.2062	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.05], 0.1831		-0.01 [-0.14, 0.12], 0.8679		-0.06 [-0.17, 0.04], 0.2365	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	2/29 (6.9)	2/54 (3.7)	2/31 (6.5)	5/111 (4.5)	4/60 (6.7)
RR [95%-CI]; p-value	0.76 [0.13, 4.32], 0.7598		0.57 [0.09, 3.88], 0.5689		0.68 [0.19, 2.42], 0.5473	
OR [95%-CI]; p-value	0.75 [0.12, 4.76], 0.7596		0.56 [0.07, 4.17], 0.5647		0.66 [0.17, 2.56], 0.5457	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7688		-0.03 [-0.13, 0.07], 0.5905		-0.02 [-0.10, 0.05], 0.5667	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.5974		0.8983		0.9395	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	0/33 (0.0)	2/65 (3.1)	1/29 (3.4)	5/123 (4.1)	1/62 (1.6)
RR [95%-CI]; p-value	3.47 [0.18, 67.11], 0.4111		0.89 [0.08, 9.45], 0.9246		2.52 [0.30, 21.11], 0.3939	
OR [95%-CI]; p-value	3.60 [0.17, 74.13], 0.3766		0.89 [0.08, 10.21], 0.9246		2.58 [0.30, 22.62], 0.3741	
RD [95%-CI]; p-value	0.04 [-0.03, 0.11], 0.3045		-0.00 [-0.08, 0.07], 0.9262		0.02 [-0.02, 0.07], 0.3057	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	0/29 (0.0)	1/54 (1.9)	0/31 (0.0)	2/111 (1.8)	0/60 (0.0)
RR [95%-CI]; p-value	1.04 [0.04, 29.96], 0.9840		1.17 [0.04, 33.80], 0.9285		2.18 [0.10, 47.58], 0.6203	
OR [95%-CI]; p-value	1.04 [0.03, 31.80], 0.9840		1.17 [0.04, 35.89], 0.9284		2.20 [0.10, 49.61], 0.6106	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9839		0.00 [-0.05, 0.06], 0.9269		0.01 [-0.02, 0.04], 0.5700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.6.s5.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.2534		0.2986		0.0795	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	9/58 (15.5)	7/33 (21.2)	16/65 (24.6)	3/29 (10.3)	25/123 (20.3)	10/62 (16.1)
RR [95%-CI]; p-value	0.73 [0.30, 1.78], 0.4914		2.38 [0.75, 7.54], 0.1405		1.26 [0.65, 2.45], 0.4967	
OR [95%-CI]; p-value	0.68 [0.23, 2.04], 0.4927		2.83 [0.75, 10.61], 0.1115		1.33 [0.59, 2.97], 0.4915	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.11], 0.5058		0.14 [-0.01, 0.30], 0.0666		0.04 [-0.07, 0.16], 0.4781	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	10/29 (34.5)	7/54 (13.0)	4/31 (12.9)	14/111 (12.6)	14/60 (23.3)
RR [95%-CI]; p-value	0.36 [0.15, 0.84], 0.0181		1.00 [0.32, 3.16], 0.9937		0.54 [0.28, 1.06], 0.0723	
OR [95%-CI]; p-value	0.27 [0.09, 0.80], 0.0145		1.01 [0.27, 3.75], 0.9937		0.47 [0.21, 1.08], 0.0706	
RD [95%-CI]; p-value	-0.22 [-0.41, -0.03], 0.0240		0.00 [-0.15, 0.15], 0.9937		-0.11 [-0.23, 0.02], 0.0890	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_6_m_pt_adr_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.2449		0.1512		0.8843	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	25/36 (69.4)	19/23 (82.6)	30/48 (62.5)	7/16 (43.8)	55/84 (65.5)	26/39 (66.7)
RR [95%-CI]; p-value	0.84 [0.63, 1.12], 0.2351		1.43 [0.79, 2.60], 0.2418		0.98 [0.75, 1.29], 0.8963	
OR [95%-CI]; p-value	0.48 [0.13, 1.74], 0.2574		2.14 [0.68, 6.75], 0.1884		0.95 [0.42, 2.12], 0.8969	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.08], 0.2322		0.19 [-0.09, 0.47], 0.1878		-0.01 [-0.19, 0.17], 0.8966	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	33/42 (78.6)	16/22 (72.7)	20/37 (54.1)	17/23 (73.9)	53/79 (67.1)	33/45 (73.3)
RR [95%-CI]; p-value	1.08 [0.80, 1.46], 0.6144		0.73 [0.50, 1.07], 0.1099		0.91 [0.72, 1.16], 0.4566	
OR [95%-CI]; p-value	1.38 [0.42, 4.53], 0.6001		0.42 [0.13, 1.29], 0.1240		0.74 [0.33, 1.67], 0.4683	
RD [95%-CI]; p-value	0.06 [-0.17, 0.28], 0.6086		-0.20 [-0.44, 0.04], 0.1060		-0.06 [-0.23, 0.10], 0.4599	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	25/37 (67.6)	15/17 (88.2)	22/34 (64.7)	13/21 (61.9)	47/71 (66.2)	28/38 (73.7)
RR [95%-CI]; p-value	0.77 [0.58, 1.02], 0.0643		1.05 [0.69, 1.59], 0.8354		0.90 [0.70, 1.16], 0.4055	
OR [95%-CI]; p-value	0.28 [0.05, 1.42], 0.1075		1.13 [0.37, 3.48], 0.8338		0.70 [0.29, 1.68], 0.4214	
RD [95%-CI]; p-value	-0.21 [-0.42, 0.01], 0.0595		0.03 [-0.23, 0.29], 0.8344		-0.07 [-0.25, 0.10], 0.4099	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.6667		0.3978		0.2948	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	3/23 (13.0)	2/48 (4.2)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.64 [0.14, 2.90], 0.5615		0.67 [0.06, 6.87], 0.7334		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.61 [0.11, 3.30], 0.5594		0.65 [0.06, 7.71], 0.7328		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.12], 0.5749		-0.02 [-0.15, 0.11], 0.7560		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	3/22 (13.6)	6/37 (16.2)	0/23 (0.0)	12/79 (15.2)	3/45 (6.7)
RR [95%-CI]; p-value	1.05 [0.29, 3.79], 0.9435		7.62 [0.45, 130.23], 0.1608		2.28 [0.68, 7.65], 0.1826	
OR [95%-CI]; p-value	1.06 [0.24, 4.70], 0.9434		8.90 [0.47, 167.57], 0.0846		2.51 [0.67, 9.41], 0.1617	
RD [95%-CI]; p-value	0.01 [-0.17, 0.18], 0.9431		0.14 [0.01, 0.27], 0.0369		0.09 [-0.02, 0.19], 0.1205	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	4/17 (23.5)	5/34 (14.7)	1/21 (4.8)	9/71 (12.7)	5/38 (13.2)
RR [95%-CI]; p-value	0.46 [0.13, 1.62], 0.2269		3.09 [0.39, 24.65], 0.2873		0.96 [0.35, 2.67], 0.9428	
OR [95%-CI]; p-value	0.39 [0.09, 1.81], 0.2217		3.45 [0.37, 31.79], 0.2505		0.96 [0.30, 3.09], 0.9429	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.10], 0.2681		0.10 [-0.05, 0.25], 0.1935		-0.00 [-0.14, 0.13], 0.9432	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.2355		0.4177		0.1185	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	3/84 (3.6)	4/39 (10.3)
RR [95%-CI]; p-value	0.43 [0.08, 2.36], 0.3282		0.33 [0.02, 5.03], 0.4275		0.35 [0.08, 1.48], 0.1533	
OR [95%-CI]; p-value	0.39 [0.06, 2.55], 0.3138		0.32 [0.02, 5.42], 0.4068		0.32 [0.07, 1.52], 0.1364	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.08], 0.3489		-0.04 [-0.17, 0.08], 0.5146		-0.07 [-0.17, 0.04], 0.2040	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	0/22 (0.0)	2/37 (5.4)	1/23 (4.3)	8/79 (10.1)	1/45 (2.2)
RR [95%-CI]; p-value	6.43 [0.38, 109.94], 0.1990		1.24 [0.12, 12.95], 0.8555		4.56 [0.59, 35.27], 0.1463	
OR [95%-CI]; p-value	7.33 [0.39, 137.80], 0.1251		1.26 [0.11, 14.70], 0.8550		4.96 [0.60, 41.00], 0.1028	
RD [95%-CI]; p-value	0.12 [-0.00, 0.24], 0.0528		0.01 [-0.10, 0.12], 0.8515		0.08 [-0.00, 0.16], 0.0506	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	1/17 (5.9)	0/34 (0.0)	3/21 (14.3)	4/71 (5.6)	4/38 (10.5)
RR [95%-CI]; p-value	1.84 [0.22, 15.23], 0.5727		0.10 [0.01, 1.93], 0.1277		0.54 [0.14, 2.02], 0.3565	
OR [95%-CI]; p-value	1.94 [0.20, 18.79], 0.5617		0.09 [0.00, 1.86], 0.0564		0.51 [0.12, 2.15], 0.3506	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5198		-0.13 [-0.28, 0.03], 0.1043		-0.05 [-0.16, 0.06], 0.3891	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.2999		0.1413		0.1952	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	5/23 (21.7)	5/48 (10.4)	0/16 (0.0)	9/84 (10.7)	5/39 (12.8)
RR [95%-CI]; p-value	0.51 [0.15, 1.71], 0.2755		3.44 [0.20, 59.59], 0.3963		0.84 [0.30, 2.33], 0.7315	
OR [95%-CI]; p-value	0.45 [0.11, 1.89], 0.2681		3.72 [0.19, 72.04], 0.3541		0.82 [0.25, 2.62], 0.7322	
RD [95%-CI]; p-value	-0.11 [-0.30, 0.09], 0.2912		0.07 [-0.05, 0.19], 0.2262		-0.02 [-0.15, 0.10], 0.7393	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	11/42 (26.2)	3/22 (13.6)	5/37 (13.5)	2/23 (8.7)	16/79 (20.3)	5/45 (11.1)
RR [95%-CI]; p-value	1.92 [0.60, 6.17], 0.2733		1.55 [0.33, 7.36], 0.5784		1.82 [0.72, 4.64], 0.2083	
OR [95%-CI]; p-value	2.25 [0.56, 9.10], 0.2485		1.64 [0.29, 9.25], 0.5719		2.03 [0.69, 5.98], 0.1919	
RD [95%-CI]; p-value	0.13 [-0.07, 0.32], 0.2083		0.05 [-0.11, 0.21], 0.5535		0.09 [-0.04, 0.22], 0.1603	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	5/37 (13.5)	2/17 (11.8)	2/34 (5.9)	5/21 (23.8)	7/71 (9.9)	7/38 (18.4)
RR [95%-CI]; p-value	1.15 [0.25, 5.34], 0.8596		0.25 [0.05, 1.16], 0.0765		0.54 [0.20, 1.41], 0.2069	
OR [95%-CI]; p-value	1.17 [0.20, 6.75], 0.8590		0.20 [0.03, 1.15], 0.0526		0.48 [0.16, 1.50], 0.2030	
RD [95%-CI]; p-value	0.02 [-0.17, 0.21], 0.8558		-0.18 [-0.38, 0.02], 0.0768		-0.09 [-0.23, 0.06], 0.2354	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.6491		0.9444		0.5375	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	2/39 (5.1)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		1.37 [0.07, 28.98], 0.8378		0.93 [0.18, 4.86], 0.9300	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		1.39 [0.06, 32.49], 0.8366		0.93 [0.16, 5.28], 0.9301	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		0.01 [-0.09, 0.11], 0.8241		-0.00 [-0.09, 0.08], 0.9310	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	0/22 (0.0)	2/37 (5.4)	0/23 (0.0)	5/79 (6.3)	0/45 (0.0)
RR [95%-CI]; p-value	3.21 [0.17, 61.40], 0.4379		2.54 [0.12, 53.94], 0.5498		5.76 [0.32, 103.02], 0.2341	
OR [95%-CI]; p-value	3.38 [0.16, 70.70], 0.4057		2.63 [0.11, 60.93], 0.5324		6.08 [0.32, 113.95], 0.1714	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3294		0.03 [-0.06, 0.13], 0.4913		0.05 [-0.01, 0.11], 0.0963	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	3/37 (8.1)	1/17 (5.9)	1/34 (2.9)	0/21 (0.0)	4/71 (5.6)	1/38 (2.6)
RR [95%-CI]; p-value	1.38 [0.15, 12.31], 0.7739		1.26 [0.04, 36.10], 0.8908		2.14 [0.25, 18.48], 0.4889	
OR [95%-CI]; p-value	1.41 [0.14, 14.65], 0.7718		1.27 [0.04, 39.64], 0.8904		2.21 [0.24, 20.50], 0.4753	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7592		0.01 [-0.08, 0.09], 0.8876		0.03 [-0.04, 0.10], 0.4261	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	NA		NA		NA	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	0/48 (0.0)	0/16 (0.0)	0/84 (0.0)	0/39 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	0/79 (0.0)	0/45 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	1/17 (5.9)	0/34 (0.0)	0/21 (0.0)	1/71 (1.4)	1/38 (2.6)
RR [95%-CI]; p-value	0.46 [0.03, 6.92], 0.5740		NA		0.54 [0.03, 8.32], 0.6552	
OR [95%-CI]; p-value	0.44 [0.03, 7.56], 0.5655		NA		0.53 [0.03, 8.69], 0.6502	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6137		NA		-0.01 [-0.07, 0.05], 0.6784	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	NA		NA		NA	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	1/23 (4.3)	0/48 (0.0)	0/16 (0.0)	0/84 (0.0)	1/39 (2.6)
RR [95%-CI]; p-value	0.32 [0.01, 9.02], 0.4998		NA		0.23 [0.01, 6.73], 0.3943	
OR [95%-CI]; p-value	0.31 [0.01, 9.49], 0.4755		NA		0.23 [0.01, 6.89], 0.3523	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.5234		NA		-0.02 [-0.07, 0.03], 0.4592	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	0/79 (0.0)	0/45 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	0/37 (0.0)	0/17 (0.0)	0/34 (0.0)	0/21 (0.0)	0/71 (0.0)	0/38 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.6240		0.2210		0.8275	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	23/36 (63.9)	18/23 (78.3)	27/48 (56.3)	6/16 (37.5)	50/84 (59.5)	24/39 (61.5)
RR [95%-CI]; p-value	0.82 [0.59, 1.13], 0.2234		1.50 [0.76, 2.96], 0.2425		0.97 [0.71, 1.31], 0.8303	
OR [95%-CI]; p-value	0.49 [0.15, 1.63], 0.2423		2.14 [0.67, 6.85], 0.1937		0.92 [0.42, 2.00], 0.8318	
RD [95%-CI]; p-value	-0.14 [-0.37, 0.09], 0.2213		0.19 [-0.09, 0.46], 0.1824		-0.02 [-0.21, 0.17], 0.8312	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	25/42 (59.5)	14/22 (63.6)	15/37 (40.5)	13/23 (56.5)	40/79 (50.6)	27/45 (60.0)
RR [95%-CI]; p-value	0.94 [0.63, 1.40], 0.7449		0.72 [0.42, 1.22], 0.2190		0.84 [0.61, 1.17], 0.3030	
OR [95%-CI]; p-value	0.84 [0.29, 2.44], 0.7488		0.52 [0.18, 1.50], 0.2277		0.68 [0.33, 1.44], 0.3142	
RD [95%-CI]; p-value	-0.04 [-0.29, 0.21], 0.7470		-0.16 [-0.42, 0.10], 0.2230		-0.09 [-0.27, 0.09], 0.3096	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	20/37 (54.1)	13/17 (76.5)	18/34 (52.9)	10/21 (47.6)	38/71 (53.5)	23/38 (60.5)
RR [95%-CI]; p-value	0.71 [0.48, 1.05], 0.0869		1.11 [0.64, 1.93], 0.7054		0.88 [0.63, 1.24], 0.4731	
OR [95%-CI]; p-value	0.36 [0.10, 1.32], 0.1166		1.24 [0.42, 3.68], 0.7013		0.75 [0.34, 1.67], 0.4826	
RD [95%-CI]; p-value	-0.22 [-0.48, 0.03], 0.0883		0.05 [-0.22, 0.32], 0.7009		-0.07 [-0.26, 0.12], 0.4790	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.3342		0.7228		0.4005	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	10/23 (43.5)	13/48 (27.1)	3/16 (18.8)	22/84 (26.2)	13/39 (33.3)
RR [95%-CI]; p-value	0.58 [0.28, 1.20], 0.1389		1.44 [0.47, 4.43], 0.5201		0.79 [0.44, 1.39], 0.4077	
OR [95%-CI]; p-value	0.43 [0.14, 1.32], 0.1385		1.61 [0.39, 6.58], 0.5050		0.71 [0.31, 1.62], 0.4139	
RD [95%-CI]; p-value	-0.18 [-0.43, 0.06], 0.1427		0.08 [-0.15, 0.31], 0.4754		-0.07 [-0.25, 0.10], 0.4245	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	18/42 (42.9)	8/22 (36.4)	11/37 (29.7)	5/23 (21.7)	29/79 (36.7)	13/45 (28.9)
RR [95%-CI]; p-value	1.18 [0.61, 2.27], 0.6224		1.37 [0.54, 3.43], 0.5049		1.27 [0.74, 2.19], 0.3865	
OR [95%-CI]; p-value	1.31 [0.45, 3.80], 0.6154		1.52 [0.45, 5.14], 0.4962		1.43 [0.65, 3.15], 0.3763	
RD [95%-CI]; p-value	0.06 [-0.19, 0.32], 0.6116		0.08 [-0.14, 0.30], 0.4841		0.08 [-0.09, 0.25], 0.3667	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	11/37 (29.7)	7/17 (41.2)	12/34 (35.3)	8/21 (38.1)	23/71 (32.4)	15/38 (39.5)
RR [95%-CI]; p-value	0.72 [0.34, 1.53], 0.3970		0.93 [0.46, 1.88], 0.8331		0.82 [0.49, 1.38], 0.4542	
OR [95%-CI]; p-value	0.60 [0.18, 2.00], 0.4073		0.89 [0.29, 2.74], 0.8338		0.73 [0.32, 1.67], 0.4598	
RD [95%-CI]; p-value	-0.11 [-0.39, 0.16], 0.4170		-0.03 [-0.29, 0.23], 0.8344		-0.07 [-0.26, 0.12], 0.4646	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
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N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.2355		0.4177		0.1185	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	3/84 (3.6)	4/39 (10.3)
RR [95%-CI]; p-value	0.43 [0.08, 2.36], 0.3282		0.33 [0.02, 5.03], 0.4275		0.35 [0.08, 1.48], 0.1533	
OR [95%-CI]; p-value	0.39 [0.06, 2.55], 0.3138		0.32 [0.02, 5.42], 0.4068		0.32 [0.07, 1.52], 0.1364	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.08], 0.3489		-0.04 [-0.17, 0.08], 0.5146		-0.07 [-0.17, 0.04], 0.2040	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	0/22 (0.0)	2/37 (5.4)	1/23 (4.3)	8/79 (10.1)	1/45 (2.2)
RR [95%-CI]; p-value	6.43 [0.38, 109.94], 0.1990		1.24 [0.12, 12.95], 0.8555		4.56 [0.59, 35.27], 0.1463	
OR [95%-CI]; p-value	7.33 [0.39, 137.80], 0.1251		1.26 [0.11, 14.70], 0.8550		4.96 [0.60, 41.00], 0.1028	
RD [95%-CI]; p-value	0.12 [-0.00, 0.24], 0.0528		0.01 [-0.10, 0.12], 0.8515		0.08 [-0.00, 0.16], 0.0506	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	1/17 (5.9)	0/34 (0.0)	3/21 (14.3)	4/71 (5.6)	4/38 (10.5)
RR [95%-CI]; p-value	1.84 [0.22, 15.23], 0.5727		0.10 [0.01, 1.93], 0.1277		0.54 [0.14, 2.02], 0.3565	
OR [95%-CI]; p-value	1.94 [0.20, 18.79], 0.5617		0.09 [0.00, 1.86], 0.0564		0.51 [0.12, 2.15], 0.3506	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5198		-0.13 [-0.28, 0.03], 0.1043		-0.05 [-0.16, 0.06], 0.3891	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.6787		0.9988		0.9101	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	3/23 (13.0)	4/48 (8.3)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.21 [0.02, 1.93], 0.1686		1.33 [0.16, 11.07], 0.7900		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.19 [0.02, 1.96], 0.1261		1.36 [0.14, 13.18], 0.7880		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.1732		0.02 [-0.12, 0.16], 0.7738		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	4/22 (18.2)	1/37 (2.7)	0/23 (0.0)	6/79 (7.6)	4/45 (8.9)
RR [95%-CI]; p-value	0.65 [0.20, 2.19], 0.4925		1.27 [0.04, 36.39], 0.8889		0.85 [0.25, 2.87], 0.7990	
OR [95%-CI]; p-value	0.61 [0.15, 2.54], 0.4927		1.28 [0.04, 39.64], 0.8885		0.84 [0.22, 3.16], 0.7992	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5142		0.01 [-0.07, 0.08], 0.8856		-0.01 [-0.11, 0.09], 0.8029	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	2/17 (11.8)	2/34 (5.9)	1/21 (4.8)	4/71 (5.6)	3/38 (7.9)
RR [95%-CI]; p-value	0.46 [0.07, 2.99], 0.4160		1.24 [0.12, 12.80], 0.8594		0.71 [0.17, 3.02], 0.6470	
OR [95%-CI]; p-value	0.43 [0.06, 3.33], 0.4073		1.25 [0.11, 14.70], 0.8589		0.70 [0.15, 3.29], 0.6463	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4624		0.01 [-0.11, 0.13], 0.8555		-0.02 [-0.12, 0.08], 0.6613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.7238		0.8795		0.8709	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	8/23 (34.8)	9/48 (18.8)	1/16 (6.3)	18/84 (21.4)	9/39 (23.1)
RR [95%-CI]; p-value	0.72 [0.32, 1.59], 0.4160		3.00 [0.41, 21.88], 0.2785		0.93 [0.46, 1.88], 0.8366	
OR [95%-CI]; p-value	0.63 [0.20, 1.96], 0.4184		3.46 [0.40, 29.72], 0.2330		0.91 [0.37, 2.26], 0.8372	
RD [95%-CI]; p-value	-0.10 [-0.34, 0.14], 0.4255		0.13 [-0.04, 0.29], 0.1306		-0.02 [-0.18, 0.14], 0.8387	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	6/37 (16.2)	2/23 (8.7)	12/79 (15.2)	6/45 (13.3)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		1.86 [0.41, 8.47], 0.4196		1.14 [0.46, 2.83], 0.7787	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		2.03 [0.37, 11.05], 0.4047		1.16 [0.40, 3.35], 0.7778	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.11, 0.15], 0.7745	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	8/34 (23.5)	3/21 (14.3)	14/71 (19.7)	9/38 (23.7)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		1.65 [0.49, 5.52], 0.4190		0.83 [0.40, 1.74], 0.6269	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		1.85 [0.43, 7.92], 0.4051		0.79 [0.31, 2.04], 0.6287	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		0.09 [-0.11, 0.30], 0.3808		-0.04 [-0.20, 0.12], 0.6352	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1454		0.2566		0.0421	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	7/23 (30.4)	5/48 (10.4)	2/16 (12.5)	8/84 (9.5)	9/39 (23.1)
RR [95%-CI]; p-value	0.27 [0.08, 0.95], 0.0418		0.83 [0.18, 3.88], 0.8164		0.41 [0.17, 0.99], 0.0470	
OR [95%-CI]; p-value	0.21 [0.05, 0.91], 0.0273		0.81 [0.14, 4.67], 0.8171		0.35 [0.12, 0.99], 0.0427	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0378		-0.02 [-0.20, 0.16], 0.8241		-0.14 [-0.28, 0.01], 0.0696	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	3/22 (13.6)	6/37 (16.2)	1/23 (4.3)	14/79 (17.7)	4/45 (8.9)
RR [95%-CI]; p-value	1.40 [0.41, 4.74], 0.5921		3.73 [0.48, 29.03], 0.2087		1.99 [0.70, 5.69], 0.1974	
OR [95%-CI]; p-value	1.49 [0.35, 6.29], 0.5858		4.26 [0.48, 37.91], 0.1638		2.21 [0.68, 7.17], 0.1794	
RD [95%-CI]; p-value	0.05 [-0.13, 0.24], 0.5689		0.12 [-0.03, 0.26], 0.1089		0.09 [-0.03, 0.21], 0.1435	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	5/17 (29.4)	3/34 (8.8)	4/21 (19.0)	7/71 (9.9)	9/38 (23.7)
RR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0972		0.46 [0.11, 1.87], 0.2795		0.42 [0.17, 1.03], 0.0579	
OR [95%-CI]; p-value	0.29 [0.07, 1.27], 0.0885		0.41 [0.08, 2.06], 0.2690		0.35 [0.12, 1.04], 0.0519	
RD [95%-CI]; p-value	-0.19 [-0.42, 0.05], 0.1265		-0.10 [-0.30, 0.09], 0.2994		-0.14 [-0.29, 0.01], 0.0745	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.2532		0.5186		0.9220	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	6/23 (26.1)	10/48 (20.8)	3/16 (18.8)	19/84 (22.6)	9/39 (23.1)
RR [95%-CI]; p-value	0.96 [0.39, 2.34], 0.9254		1.11 [0.35, 3.54], 0.8587		0.98 [0.49, 1.97], 0.9550	
OR [95%-CI]; p-value	0.94 [0.29, 3.13], 0.9255		1.14 [0.27, 4.79], 0.8576		0.97 [0.39, 2.40], 0.9551	
RD [95%-CI]; p-value	-0.01 [-0.24, 0.22], 0.9257		0.02 [-0.20, 0.24], 0.8548		-0.00 [-0.16, 0.16], 0.9552	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	15/42 (35.7)	5/22 (22.7)	8/37 (21.6)	7/23 (30.4)	23/79 (29.1)	12/45 (26.7)
RR [95%-CI]; p-value	1.57 [0.66, 3.75], 0.3090		0.71 [0.30, 1.70], 0.4415		1.09 [0.60, 1.98], 0.7721	
OR [95%-CI]; p-value	1.89 [0.58, 6.15], 0.2870		0.63 [0.19, 2.06], 0.4434		1.13 [0.50, 2.56], 0.7710	
RD [95%-CI]; p-value	0.13 [-0.10, 0.36], 0.2628		-0.09 [-0.32, 0.14], 0.4529		0.02 [-0.14, 0.19], 0.7692	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	6/17 (35.3)	10/34 (29.4)	4/21 (19.0)	17/71 (23.9)	10/38 (26.3)
RR [95%-CI]; p-value	0.54 [0.21, 1.35], 0.1873		1.54 [0.55, 4.30], 0.4057		0.91 [0.46, 1.79], 0.7837	
OR [95%-CI]; p-value	0.43 [0.12, 1.56], 0.1911		1.77 [0.48, 6.60], 0.3913		0.88 [0.36, 2.18], 0.7846	
RD [95%-CI]; p-value	-0.16 [-0.42, 0.10], 0.2168		0.10 [-0.12, 0.33], 0.3715		-0.02 [-0.20, 0.15], 0.7865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2926		0.3399		0.1560	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	4/23 (17.4)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.06, 1.61], 0.1660		0.83 [0.18, 3.88], 0.8164		0.54 [0.19, 1.51], 0.2397	
OR [95%-CI]; p-value	0.28 [0.05, 1.67], 0.1424		0.81 [0.14, 4.67], 0.8171		0.50 [0.16, 1.60], 0.2366	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1775		-0.02 [-0.20, 0.16], 0.8241		-0.07 [-0.20, 0.06], 0.2793	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	1/22 (4.5)	5/37 (13.5)	1/23 (4.3)	10/79 (12.7)	2/45 (4.4)
RR [95%-CI]; p-value	2.62 [0.33, 21.05], 0.3652		3.11 [0.39, 24.95], 0.2860		2.85 [0.65, 12.43], 0.1638	
OR [95%-CI]; p-value	2.84 [0.31, 25.94], 0.3374		3.44 [0.38, 31.48], 0.2499		3.12 [0.65, 14.91], 0.1369	
RD [95%-CI]; p-value	0.07 [-0.06, 0.20], 0.2710		0.09 [-0.05, 0.23], 0.1934		0.08 [-0.01, 0.18], 0.0897	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	5/17 (29.4)	1/34 (2.9)	2/21 (9.5)	8/71 (11.3)	7/38 (18.4)
RR [95%-CI]; p-value	0.64 [0.24, 1.74], 0.3841		0.31 [0.03, 3.20], 0.3246		0.61 [0.24, 1.56], 0.3027	
OR [95%-CI]; p-value	0.56 [0.15, 2.11], 0.3890		0.29 [0.02, 3.39], 0.2963		0.56 [0.19, 1.69], 0.3016	
RD [95%-CI]; p-value	-0.10 [-0.36, 0.15], 0.4120		-0.07 [-0.20, 0.07], 0.3491		-0.07 [-0.22, 0.07], 0.3287	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.1513		0.2896		0.3517	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	9/23 (39.1)	8/48 (16.7)	2/16 (12.5)	12/84 (14.3)	11/39 (28.2)
RR [95%-CI]; p-value	0.28 [0.10, 0.82], 0.0194		1.33 [0.32, 5.64], 0.6959		0.51 [0.25, 1.05], 0.0658	
OR [95%-CI]; p-value	0.19 [0.05, 0.74], 0.0113		1.40 [0.26, 7.40], 0.6910		0.42 [0.17, 1.07], 0.0654	
RD [95%-CI]; p-value	-0.28 [-0.50, -0.06], 0.0144		0.04 [-0.15, 0.23], 0.6727		-0.14 [-0.30, 0.02], 0.0878	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	11/42 (26.2)	7/22 (31.8)	6/37 (16.2)	2/23 (8.7)	17/79 (21.5)	9/45 (20.0)
RR [95%-CI]; p-value	0.82 [0.37, 1.82], 0.6313		1.86 [0.41, 8.47], 0.4196		1.08 [0.52, 2.21], 0.8421	
OR [95%-CI]; p-value	0.76 [0.25, 2.36], 0.6344		2.03 [0.37, 11.05], 0.4047		1.10 [0.44, 2.71], 0.8416	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.18], 0.6398		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.13, 0.16], 0.8405	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	8/37 (21.6)	3/17 (17.6)	7/34 (20.6)	8/21 (38.1)	15/71 (21.1)	11/38 (28.9)
RR [95%-CI]; p-value	1.23 [0.37, 4.05], 0.7393		0.54 [0.23, 1.27], 0.1589		0.73 [0.37, 1.43], 0.3576	
OR [95%-CI]; p-value	1.29 [0.30, 5.61], 0.7363		0.42 [0.13, 1.41], 0.1567		0.66 [0.27, 1.62], 0.3613	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7287		-0.18 [-0.42, 0.07], 0.1669		-0.08 [-0.25, 0.09], 0.3746	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2515		0.2613		0.0816	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	10/36 (27.8)	7/23 (30.4)	12/48 (25.0)	3/16 (18.8)	22/84 (26.2)	10/39 (25.6)
RR [95%-CI]; p-value	0.91 [0.41, 2.06], 0.8255		1.33 [0.43, 4.13], 0.6183		1.02 [0.54, 1.94], 0.9485	
OR [95%-CI]; p-value	0.88 [0.28, 2.77], 0.8260		1.44 [0.35, 5.95], 0.6093		1.03 [0.43, 2.45], 0.9485	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.21], 0.8270		0.06 [-0.16, 0.29], 0.5896		0.01 [-0.16, 0.17], 0.9483	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	4/42 (9.5)	7/22 (31.8)	4/37 (10.8)	7/23 (30.4)	8/79 (10.1)	14/45 (31.1)
RR [95%-CI]; p-value	0.30 [0.10, 0.91], 0.0340		0.36 [0.12, 1.08], 0.0683		0.33 [0.15, 0.72], 0.0052	
OR [95%-CI]; p-value	0.23 [0.06, 0.88], 0.0247		0.28 [0.07, 1.09], 0.0561		0.25 [0.09, 0.66], 0.0033	
RD [95%-CI]; p-value	-0.22 [-0.44, -0.01], 0.0411		-0.20 [-0.41, 0.02], 0.0710		-0.21 [-0.36, -0.06], 0.0064	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	4/34 (11.8)	4/21 (19.0)	10/71 (14.1)	10/38 (26.3)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		0.62 [0.17, 2.21], 0.4588		0.54 [0.24, 1.17], 0.1177	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		0.57 [0.13, 2.56], 0.4567		0.46 [0.17, 1.23], 0.1159	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		-0.07 [-0.27, 0.13], 0.4750		-0.12 [-0.28, 0.04], 0.1382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8116		0.5748		0.5975	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	4/23 (17.4)	5/48 (10.4)	0/16 (0.0)	9/84 (10.7)	4/39 (10.3)
RR [95%-CI]; p-value	0.64 [0.18, 2.31], 0.4938		3.44 [0.20, 59.59], 0.3963		1.04 [0.34, 3.19], 0.9388	
OR [95%-CI]; p-value	0.59 [0.13, 2.65], 0.4920		3.72 [0.19, 72.04], 0.3541		1.05 [0.30, 3.64], 0.9387	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5077		0.07 [-0.05, 0.19], 0.2262		0.00 [-0.11, 0.12], 0.9383	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	6/22 (27.3)	3/37 (8.1)	3/23 (13.0)	8/79 (10.1)	9/45 (20.0)
RR [95%-CI]; p-value	0.44 [0.15, 1.27], 0.1285		0.62 [0.14, 2.82], 0.5381		0.51 [0.21, 1.22], 0.1292	
OR [95%-CI]; p-value	0.36 [0.10, 1.35], 0.1217		0.59 [0.11, 3.20], 0.5355		0.45 [0.16, 1.27], 0.1243	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.06], 0.1521		-0.05 [-0.21, 0.11], 0.5537		-0.10 [-0.23, 0.04], 0.1501	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	5/34 (14.7)	4/21 (19.0)	7/71 (9.9)	5/38 (13.2)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.77 [0.23, 2.56], 0.6719		0.75 [0.25, 2.20], 0.5997	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.73 [0.17, 3.11], 0.6724		0.72 [0.21, 2.45], 0.6000	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.04 [-0.25, 0.16], 0.6793		-0.03 [-0.16, 0.09], 0.6132	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.2959		0.7912		0.4360	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	4/23 (17.4)	1/48 (2.1)	0/16 (0.0)	2/84 (2.4)	4/39 (10.3)
RR [95%-CI]; p-value	0.16 [0.02, 1.34], 0.0911		0.69 [0.02, 19.56], 0.8264		0.23 [0.04, 1.21], 0.0836	
OR [95%-CI]; p-value	0.14 [0.01, 1.30], 0.0493		0.68 [0.02, 21.27], 0.8257		0.21 [0.04, 1.22], 0.0592	
RD [95%-CI]; p-value	-0.15 [-0.31, 0.02], 0.0806		-0.01 [-0.10, 0.08], 0.8402		-0.08 [-0.18, 0.02], 0.1251	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	2/22 (9.1)	3/37 (8.1)	1/23 (4.3)	3/79 (3.8)	3/45 (6.7)
RR [95%-CI]; p-value	0.13 [0.01, 2.75], 0.1897		1.86 [0.21, 16.87], 0.5792		0.57 [0.12, 2.70], 0.4789	
OR [95%-CI]; p-value	0.12 [0.01, 2.76], 0.1185		1.94 [0.19, 19.87], 0.5702		0.55 [0.11, 2.86], 0.4740	
RD [95%-CI]; p-value	-0.08 [-0.20, 0.05], 0.2125		0.04 [-0.08, 0.16], 0.5430		-0.03 [-0.11, 0.06], 0.5042	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	3/37 (8.1)	1/17 (5.9)	1/34 (2.9)	1/21 (4.8)	4/71 (5.6)	2/38 (5.3)
RR [95%-CI]; p-value	1.38 [0.15, 12.31], 0.7739		0.62 [0.04, 9.36], 0.7282		1.07 [0.21, 5.58], 0.9356	
OR [95%-CI]; p-value	1.41 [0.14, 14.65], 0.7718		0.61 [0.04, 10.24], 0.7260		1.07 [0.19, 6.15], 0.9356	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7592		-0.02 [-0.13, 0.09], 0.7395		0.00 [-0.09, 0.09], 0.9349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1068		0.1759		0.1507	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	6/23 (26.1)	8/48 (16.7)	0/16 (0.0)	11/84 (13.1)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.09, 1.15], 0.0814		5.50 [0.33, 90.61], 0.2331		0.85 [0.34, 2.13], 0.7312	
OR [95%-CI]; p-value	0.26 [0.06, 1.16], 0.0643		6.40 [0.35, 118.11], 0.1578		0.83 [0.28, 2.43], 0.7321	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.02], 0.0832		0.14 [0.00, 0.27], 0.0461		-0.02 [-0.16, 0.11], 0.7382	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	1/22 (4.5)	4/37 (10.8)	2/23 (8.7)	12/79 (15.2)	3/45 (6.7)
RR [95%-CI]; p-value	4.19 [0.56, 31.40], 0.1632		1.24 [0.25, 6.25], 0.7917		2.28 [0.68, 7.65], 0.1826	
OR [95%-CI]; p-value	4.94 [0.58, 42.37], 0.1129		1.27 [0.21, 7.57], 0.7906		2.51 [0.67, 9.41], 0.1617	
RD [95%-CI]; p-value	0.15 [-0.00, 0.29], 0.0536		0.02 [-0.13, 0.17], 0.7858		0.09 [-0.02, 0.19], 0.1205	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	3/17 (17.6)	1/34 (2.9)	3/21 (14.3)	5/71 (7.0)	6/38 (15.8)
RR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4872		0.21 [0.02, 1.85], 0.1585		0.45 [0.15, 1.37], 0.1575	
OR [95%-CI]; p-value	0.57 [0.11, 2.86], 0.4873		0.18 [0.02, 1.88], 0.1155		0.40 [0.11, 1.42], 0.1485	
RD [95%-CI]; p-value	-0.07 [-0.28, 0.14], 0.5175		-0.11 [-0.27, 0.05], 0.1648		-0.09 [-0.22, 0.04], 0.1883	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3647		0.8073		0.3635	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	5/23 (21.7)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	7/39 (17.9)
RR [95%-CI]; p-value	0.26 [0.05, 1.21], 0.0853		0.83 [0.18, 3.88], 0.8164		0.46 [0.17, 1.23], 0.1235	
OR [95%-CI]; p-value	0.21 [0.04, 1.20], 0.0608		0.81 [0.14, 4.67], 0.8171		0.42 [0.13, 1.28], 0.1182	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0855		-0.02 [-0.20, 0.16], 0.8241		-0.10 [-0.23, 0.04], 0.1601	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	1/22 (4.5)	3/37 (8.1)	1/23 (4.3)	6/79 (7.6)	2/45 (4.4)
RR [95%-CI]; p-value	1.57 [0.17, 14.23], 0.6877		1.86 [0.21, 16.87], 0.5792		1.71 [0.36, 8.11], 0.5002	
OR [95%-CI]; p-value	1.62 [0.16, 16.51], 0.6835		1.94 [0.19, 19.87], 0.5702		1.77 [0.34, 9.15], 0.4923	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6629		0.04 [-0.08, 0.16], 0.5430		0.03 [-0.05, 0.12], 0.4617	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	2/17 (11.8)	4/34 (11.8)	3/21 (14.3)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.23 [0.02, 2.36], 0.2161		0.82 [0.20, 3.32], 0.7850		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.21 [0.02, 2.48], 0.1769		0.80 [0.16, 3.99], 0.7852		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2724		-0.03 [-0.21, 0.16], 0.7891		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.9915		0.2242		0.2183	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.85 [0.21, 3.46], 0.8227		0.33 [0.02, 5.03], 0.4275		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.83 [0.17, 4.12], 0.8229		0.32 [0.02, 5.42], 0.4068		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.15], 0.8254		-0.04 [-0.17, 0.08], 0.5146		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	3/37 (8.1)	0/23 (0.0)	9/79 (11.4)	4/45 (8.9)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		3.81 [0.20, 72.73], 0.3739		1.28 [0.42, 3.93], 0.6640	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		4.06 [0.19, 84.88], 0.3315		1.32 [0.38, 4.55], 0.6617	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.06 [-0.05, 0.17], 0.2668		0.03 [-0.08, 0.13], 0.6518	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	2/34 (5.9)	6/21 (28.6)	4/71 (5.6)	7/38 (18.4)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.21 [0.05, 0.93], 0.0396		0.31 [0.10, 0.98], 0.0460	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.16 [0.03, 0.87], 0.0204		0.26 [0.07, 0.97], 0.0347	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.23 [-0.44, -0.02], 0.0332		-0.13 [-0.26, 0.01], 0.0622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.3.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9802		0.8567		0.7960	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	6/23 (26.1)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	6/39 (15.4)
RR [95%-CI]; p-value	0.21 [0.05, 0.97], 0.0450		1.37 [0.07, 28.98], 0.8378		0.31 [0.09, 1.03], 0.0568	
OR [95%-CI]; p-value	0.17 [0.03, 0.91], 0.0247		1.39 [0.06, 32.49], 0.8366		0.28 [0.07, 1.04], 0.0449	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.01], 0.0385		0.01 [-0.09, 0.11], 0.8241		-0.11 [-0.23, 0.02], 0.0880	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	1/22 (4.5)	1/37 (2.7)	0/23 (0.0)	1/79 (1.3)	1/45 (2.2)
RR [95%-CI]; p-value	0.26 [0.01, 7.42], 0.4298		1.27 [0.04, 36.39], 0.8889		0.57 [0.04, 8.89], 0.6881	
OR [95%-CI]; p-value	0.25 [0.01, 7.76], 0.3947		1.28 [0.04, 39.64], 0.8885		0.56 [0.03, 9.24], 0.6844	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.06], 0.4771		0.01 [-0.07, 0.08], 0.8856		-0.01 [-0.06, 0.04], 0.7056	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	5/17 (29.4)	3/34 (8.8)	0/21 (0.0)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.18 [0.04, 0.85], 0.0306		3.79 [0.20, 72.11], 0.3748		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.14 [0.02, 0.80], 0.0147		4.06 [0.19, 85.37], 0.3320		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.24 [-0.47, -0.01], 0.0395		0.06 [-0.05, 0.18], 0.2667		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_3_m_pt_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.3.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5486		0.5916		0.6215	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	2/39 (5.1)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		1.37 [0.07, 28.98], 0.8378		0.93 [0.18, 4.86], 0.9300	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		1.39 [0.06, 32.49], 0.8366		0.93 [0.16, 5.28], 0.9301	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		0.01 [-0.09, 0.11], 0.8241		-0.00 [-0.09, 0.08], 0.9310	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	1/42 (2.4)	3/22 (13.6)	2/37 (5.4)	2/23 (8.7)	3/79 (3.8)	5/45 (11.1)
RR [95%-CI]; p-value	0.17 [0.02, 1.58], 0.1206		0.62 [0.09, 4.11], 0.6219		0.34 [0.09, 1.36], 0.1283	
OR [95%-CI]; p-value	0.15 [0.02, 1.58], 0.0773		0.60 [0.08, 4.58], 0.6194		0.32 [0.07, 1.39], 0.1109	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1431		-0.03 [-0.17, 0.10], 0.6360		-0.07 [-0.17, 0.03], 0.1560	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	3/17 (17.6)	3/34 (8.8)	0/21 (0.0)	4/71 (5.6)	3/38 (7.9)
RR [95%-CI]; p-value	0.15 [0.02, 1.37], 0.0930		3.79 [0.20, 72.11], 0.3748		0.71 [0.17, 3.02], 0.6470	
OR [95%-CI]; p-value	0.13 [0.01, 1.35], 0.0515		4.06 [0.19, 85.37], 0.3320		0.70 [0.15, 3.29], 0.6463	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.04], 0.1204		0.06 [-0.05, 0.18], 0.2667		-0.02 [-0.12, 0.08], 0.6613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_3_m_pt_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.3.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.7111		0.3669		0.1460	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	0/48 (0.0)	1/16 (6.3)	2/84 (2.4)	3/39 (7.7)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		0.16 [0.01, 4.69], 0.2913		0.31 [0.05, 1.78], 0.1886	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		0.16 [0.00, 4.89], 0.2297		0.29 [0.05, 1.83], 0.1651	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		-0.05 [-0.17, 0.07], 0.4016		-0.05 [-0.14, 0.04], 0.2461	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	4/42 (9.5)	1/22 (4.5)	2/37 (5.4)	0/23 (0.0)	6/79 (7.6)	1/45 (2.2)
RR [95%-CI]; p-value	2.10 [0.25, 17.63], 0.4961		2.54 [0.12, 53.94], 0.5498		3.42 [0.42, 27.50], 0.2480	
OR [95%-CI]; p-value	2.21 [0.23, 21.08], 0.4809		2.63 [0.11, 60.93], 0.5324		3.62 [0.42, 31.04], 0.2126	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.4326		0.03 [-0.06, 0.13], 0.4913		0.05 [-0.02, 0.13], 0.1468	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	2/34 (5.9)	5/21 (23.8)	4/71 (5.6)	6/38 (15.8)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.25 [0.05, 1.16], 0.0765		0.36 [0.11, 1.19], 0.0929	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.20 [0.03, 1.15], 0.0526		0.32 [0.08, 1.21], 0.0801	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.18 [-0.38, 0.02], 0.0768		-0.10 [-0.23, 0.03], 0.1192	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_3_m_pt_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.8.1.1.s6.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8565		0.7924		0.8330	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	1/23 (4.3)	1/48 (2.1)	0/16 (0.0)	1/84 (1.2)	1/39 (2.6)
RR [95%-CI]; p-value	0.32 [0.01, 9.02], 0.4998		0.69 [0.02, 19.56], 0.8264		0.46 [0.03, 7.23], 0.5839	
OR [95%-CI]; p-value	0.31 [0.01, 9.49], 0.4755		0.68 [0.02, 21.27], 0.8257		0.46 [0.03, 7.52], 0.5751	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.5234		-0.01 [-0.10, 0.08], 0.8402		-0.01 [-0.07, 0.04], 0.6230	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	1/42 (2.4)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	1/79 (1.3)	0/45 (0.0)
RR [95%-CI]; p-value	1.07 [0.04, 30.72], 0.9679		0.63 [0.01, 30.52], 0.8137		1.15 [0.04, 33.67], 0.9346	
OR [95%-CI]; p-value	1.07 [0.03, 33.27], 0.9678		0.62 [0.01, 32.42], 0.8121		1.15 [0.04, 35.08], 0.9345	
RD [95%-CI]; p-value	0.00 [-0.07, 0.08], 0.9675		-0.01 [-0.08, 0.06], 0.8213		0.00 [-0.04, 0.04], 0.9332	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	1/34 (2.9)	3/21 (14.3)	2/71 (2.8)	3/38 (7.9)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		0.21 [0.02, 1.85], 0.1585		0.36 [0.06, 2.04], 0.2471	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		0.18 [0.02, 1.88], 0.1155		0.34 [0.05, 2.12], 0.2272	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		-0.11 [-0.27, 0.05], 0.1648		-0.05 [-0.14, 0.04], 0.2896	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_8_1_1_m_soc_sae5pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.8.1.2.s6.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_8_1_2_m_pt_sae5pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.5.1.1.s6.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_5_1_1_m_soc_aeg35pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.5.1.2.s6.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_5_1_2_m_pt_aeg35pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.7238		0.8795		0.8709	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	8/23 (34.8)	9/48 (18.8)	1/16 (6.3)	18/84 (21.4)	9/39 (23.1)
RR [95%-CI]; p-value	0.72 [0.32, 1.59], 0.4160		3.00 [0.41, 21.88], 0.2785		0.93 [0.46, 1.88], 0.8366	
OR [95%-CI]; p-value	0.63 [0.20, 1.96], 0.4184		3.46 [0.40, 29.72], 0.2330		0.91 [0.37, 2.26], 0.8372	
RD [95%-CI]; p-value	-0.10 [-0.34, 0.14], 0.4255		0.13 [-0.04, 0.29], 0.1306		-0.02 [-0.18, 0.14], 0.8387	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	6/37 (16.2)	2/23 (8.7)	12/79 (15.2)	6/45 (13.3)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		1.86 [0.41, 8.47], 0.4196		1.14 [0.46, 2.83], 0.7787	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		2.03 [0.37, 11.05], 0.4047		1.16 [0.40, 3.35], 0.7778	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.11, 0.15], 0.7745	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	8/34 (23.5)	3/21 (14.3)	14/71 (19.7)	9/38 (23.7)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		1.65 [0.49, 5.52], 0.4190		0.83 [0.40, 1.74], 0.6269	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		1.85 [0.43, 7.92], 0.4051		0.79 [0.31, 2.04], 0.6287	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		0.09 [-0.11, 0.30], 0.3808		-0.04 [-0.20, 0.12], 0.6352	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1454		0.2566		0.0421	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	7/23 (30.4)	5/48 (10.4)	2/16 (12.5)	8/84 (9.5)	9/39 (23.1)
RR [95%-CI]; p-value	0.27 [0.08, 0.95], 0.0418		0.83 [0.18, 3.88], 0.8164		0.41 [0.17, 0.99], 0.0470	
OR [95%-CI]; p-value	0.21 [0.05, 0.91], 0.0273		0.81 [0.14, 4.67], 0.8171		0.35 [0.12, 0.99], 0.0427	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0378		-0.02 [-0.20, 0.16], 0.8241		-0.14 [-0.28, 0.01], 0.0696	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	3/22 (13.6)	6/37 (16.2)	1/23 (4.3)	14/79 (17.7)	4/45 (8.9)
RR [95%-CI]; p-value	1.40 [0.41, 4.74], 0.5921		3.73 [0.48, 29.03], 0.2087		1.99 [0.70, 5.69], 0.1974	
OR [95%-CI]; p-value	1.49 [0.35, 6.29], 0.5858		4.26 [0.48, 37.91], 0.1638		2.21 [0.68, 7.17], 0.1794	
RD [95%-CI]; p-value	0.05 [-0.13, 0.24], 0.5689		0.12 [-0.03, 0.26], 0.1089		0.09 [-0.03, 0.21], 0.1435	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	5/17 (29.4)	3/34 (8.8)	4/21 (19.0)	7/71 (9.9)	9/38 (23.7)
RR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0972		0.46 [0.11, 1.87], 0.2795		0.42 [0.17, 1.03], 0.0579	
OR [95%-CI]; p-value	0.29 [0.07, 1.27], 0.0885		0.41 [0.08, 2.06], 0.2690		0.35 [0.12, 1.04], 0.0519	
RD [95%-CI]; p-value	-0.19 [-0.42, 0.05], 0.1265		-0.10 [-0.30, 0.09], 0.2994		-0.14 [-0.29, 0.01], 0.0745	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.2532		0.5186		0.9220	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	6/23 (26.1)	10/48 (20.8)	3/16 (18.8)	19/84 (22.6)	9/39 (23.1)
RR [95%-CI]; p-value	0.96 [0.39, 2.34], 0.9254		1.11 [0.35, 3.54], 0.8587		0.98 [0.49, 1.97], 0.9550	
OR [95%-CI]; p-value	0.94 [0.29, 3.13], 0.9255		1.14 [0.27, 4.79], 0.8576		0.97 [0.39, 2.40], 0.9551	
RD [95%-CI]; p-value	-0.01 [-0.24, 0.22], 0.9257		0.02 [-0.20, 0.24], 0.8548		-0.00 [-0.16, 0.16], 0.9552	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	15/42 (35.7)	5/22 (22.7)	8/37 (21.6)	7/23 (30.4)	23/79 (29.1)	12/45 (26.7)
RR [95%-CI]; p-value	1.57 [0.66, 3.75], 0.3090		0.71 [0.30, 1.70], 0.4415		1.09 [0.60, 1.98], 0.7721	
OR [95%-CI]; p-value	1.89 [0.58, 6.15], 0.2870		0.63 [0.19, 2.06], 0.4434		1.13 [0.50, 2.56], 0.7710	
RD [95%-CI]; p-value	0.13 [-0.10, 0.36], 0.2628		-0.09 [-0.32, 0.14], 0.4529		0.02 [-0.14, 0.19], 0.7692	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	6/17 (35.3)	10/34 (29.4)	4/21 (19.0)	17/71 (23.9)	10/38 (26.3)
RR [95%-CI]; p-value	0.54 [0.21, 1.35], 0.1873		1.54 [0.55, 4.30], 0.4057		0.91 [0.46, 1.79], 0.7837	
OR [95%-CI]; p-value	0.43 [0.12, 1.56], 0.1911		1.77 [0.48, 6.60], 0.3913		0.88 [0.36, 2.18], 0.7846	
RD [95%-CI]; p-value	-0.16 [-0.42, 0.10], 0.2168		0.10 [-0.12, 0.33], 0.3715		-0.02 [-0.20, 0.15], 0.7865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.5867		0.6743		0.3149	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	2/48 (4.2)	1/16 (6.3)	4/84 (4.8)	3/39 (7.7)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		0.67 [0.06, 6.87], 0.7334		0.62 [0.15, 2.63], 0.5162	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		0.65 [0.06, 7.71], 0.7328		0.60 [0.13, 2.82], 0.5139	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		-0.02 [-0.15, 0.11], 0.7560		-0.03 [-0.12, 0.07], 0.5464	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	3/22 (13.6)	2/37 (5.4)	0/23 (0.0)	7/79 (8.9)	3/45 (6.7)
RR [95%-CI]; p-value	0.87 [0.23, 3.32], 0.8420		2.54 [0.12, 53.94], 0.5498		1.33 [0.36, 4.89], 0.6684	
OR [95%-CI]; p-value	0.86 [0.18, 3.97], 0.8423		2.63 [0.11, 60.93], 0.5324		1.36 [0.33, 5.55], 0.6661	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.16], 0.8451		0.03 [-0.06, 0.13], 0.4913		0.02 [-0.07, 0.12], 0.6546	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	0/17 (0.0)	4/34 (11.8)	1/21 (4.8)	8/71 (11.3)	1/38 (2.6)
RR [95%-CI]; p-value	3.78 [0.21, 67.70], 0.3659		2.47 [0.30, 20.64], 0.4037		4.28 [0.56, 32.97], 0.1626	
OR [95%-CI]; p-value	4.12 [0.21, 82.58], 0.3192		2.67 [0.28, 25.64], 0.3801		4.70 [0.57, 39.07], 0.1185	
RD [95%-CI]; p-value	0.08 [-0.05, 0.21], 0.2193		0.07 [-0.07, 0.21], 0.3321		0.09 [-0.00, 0.18], 0.0584	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2926		0.3399		0.1560	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	4/23 (17.4)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.06, 1.61], 0.1660		0.83 [0.18, 3.88], 0.8164		0.54 [0.19, 1.51], 0.2397	
OR [95%-CI]; p-value	0.28 [0.05, 1.67], 0.1424		0.81 [0.14, 4.67], 0.8171		0.50 [0.16, 1.60], 0.2366	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1775		-0.02 [-0.20, 0.16], 0.8241		-0.07 [-0.20, 0.06], 0.2793	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	1/22 (4.5)	5/37 (13.5)	1/23 (4.3)	10/79 (12.7)	2/45 (4.4)
RR [95%-CI]; p-value	2.62 [0.33, 21.05], 0.3652		3.11 [0.39, 24.95], 0.2860		2.85 [0.65, 12.43], 0.1638	
OR [95%-CI]; p-value	2.84 [0.31, 25.94], 0.3374		3.44 [0.38, 31.48], 0.2499		3.12 [0.65, 14.91], 0.1369	
RD [95%-CI]; p-value	0.07 [-0.06, 0.20], 0.2710		0.09 [-0.05, 0.23], 0.1934		0.08 [-0.01, 0.18], 0.0897	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	5/17 (29.4)	1/34 (2.9)	2/21 (9.5)	8/71 (11.3)	7/38 (18.4)
RR [95%-CI]; p-value	0.64 [0.24, 1.74], 0.3841		0.31 [0.03, 3.20], 0.3246		0.61 [0.24, 1.56], 0.3027	
OR [95%-CI]; p-value	0.56 [0.15, 2.11], 0.3890		0.29 [0.02, 3.39], 0.2963		0.56 [0.19, 1.69], 0.3016	
RD [95%-CI]; p-value	-0.10 [-0.36, 0.15], 0.4120		-0.07 [-0.20, 0.07], 0.3491		-0.07 [-0.22, 0.07], 0.3287	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.1513		0.2896		0.3517	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	9/23 (39.1)	8/48 (16.7)	2/16 (12.5)	12/84 (14.3)	11/39 (28.2)
RR [95%-CI]; p-value	0.28 [0.10, 0.82], 0.0194		1.33 [0.32, 5.64], 0.6959		0.51 [0.25, 1.05], 0.0658	
OR [95%-CI]; p-value	0.19 [0.05, 0.74], 0.0113		1.40 [0.26, 7.40], 0.6910		0.42 [0.17, 1.07], 0.0654	
RD [95%-CI]; p-value	-0.28 [-0.50, -0.06], 0.0144		0.04 [-0.15, 0.23], 0.6727		-0.14 [-0.30, 0.02], 0.0878	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	11/42 (26.2)	7/22 (31.8)	6/37 (16.2)	2/23 (8.7)	17/79 (21.5)	9/45 (20.0)
RR [95%-CI]; p-value	0.82 [0.37, 1.82], 0.6313		1.86 [0.41, 8.47], 0.4196		1.08 [0.52, 2.21], 0.8421	
OR [95%-CI]; p-value	0.76 [0.25, 2.36], 0.6344		2.03 [0.37, 11.05], 0.4047		1.10 [0.44, 2.71], 0.8416	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.18], 0.6398		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.13, 0.16], 0.8405	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	8/37 (21.6)	3/17 (17.6)	7/34 (20.6)	8/21 (38.1)	15/71 (21.1)	11/38 (28.9)
RR [95%-CI]; p-value	1.23 [0.37, 4.05], 0.7393		0.54 [0.23, 1.27], 0.1589		0.73 [0.37, 1.43], 0.3576	
OR [95%-CI]; p-value	1.29 [0.30, 5.61], 0.7363		0.42 [0.13, 1.41], 0.1567		0.66 [0.27, 1.62], 0.3613	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7287		-0.18 [-0.42, 0.07], 0.1669		-0.08 [-0.25, 0.09], 0.3746	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2515		0.2613		0.0816	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	10/36 (27.8)	7/23 (30.4)	12/48 (25.0)	3/16 (18.8)	22/84 (26.2)	10/39 (25.6)
RR [95%-CI]; p-value	0.91 [0.41, 2.06], 0.8255		1.33 [0.43, 4.13], 0.6183		1.02 [0.54, 1.94], 0.9485	
OR [95%-CI]; p-value	0.88 [0.28, 2.77], 0.8260		1.44 [0.35, 5.95], 0.6093		1.03 [0.43, 2.45], 0.9485	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.21], 0.8270		0.06 [-0.16, 0.29], 0.5896		0.01 [-0.16, 0.17], 0.9483	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	4/42 (9.5)	7/22 (31.8)	4/37 (10.8)	7/23 (30.4)	8/79 (10.1)	14/45 (31.1)
RR [95%-CI]; p-value	0.30 [0.10, 0.91], 0.0340		0.36 [0.12, 1.08], 0.0683		0.33 [0.15, 0.72], 0.0052	
OR [95%-CI]; p-value	0.23 [0.06, 0.88], 0.0247		0.28 [0.07, 1.09], 0.0561		0.25 [0.09, 0.66], 0.0033	
RD [95%-CI]; p-value	-0.22 [-0.44, -0.01], 0.0411		-0.20 [-0.41, 0.02], 0.0710		-0.21 [-0.36, -0.06], 0.0064	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	4/34 (11.8)	4/21 (19.0)	10/71 (14.1)	10/38 (26.3)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		0.62 [0.17, 2.21], 0.4588		0.54 [0.24, 1.17], 0.1177	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		0.57 [0.13, 2.56], 0.4567		0.46 [0.17, 1.23], 0.1159	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		-0.07 [-0.27, 0.13], 0.4750		-0.12 [-0.28, 0.04], 0.1382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8116		0.5748		0.5975	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	4/23 (17.4)	5/48 (10.4)	0/16 (0.0)	9/84 (10.7)	4/39 (10.3)
RR [95%-CI]; p-value	0.64 [0.18, 2.31], 0.4938		3.44 [0.20, 59.59], 0.3963		1.04 [0.34, 3.19], 0.9388	
OR [95%-CI]; p-value	0.59 [0.13, 2.65], 0.4920		3.72 [0.19, 72.04], 0.3541		1.05 [0.30, 3.64], 0.9387	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5077		0.07 [-0.05, 0.19], 0.2262		0.00 [-0.11, 0.12], 0.9383	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	6/22 (27.3)	3/37 (8.1)	3/23 (13.0)	8/79 (10.1)	9/45 (20.0)
RR [95%-CI]; p-value	0.44 [0.15, 1.27], 0.1285		0.62 [0.14, 2.82], 0.5381		0.51 [0.21, 1.22], 0.1292	
OR [95%-CI]; p-value	0.36 [0.10, 1.35], 0.1217		0.59 [0.11, 3.20], 0.5355		0.45 [0.16, 1.27], 0.1243	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.06], 0.1521		-0.05 [-0.21, 0.11], 0.5537		-0.10 [-0.23, 0.04], 0.1501	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	5/34 (14.7)	4/21 (19.0)	7/71 (9.9)	5/38 (13.2)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.77 [0.23, 2.56], 0.6719		0.75 [0.25, 2.20], 0.5997	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.73 [0.17, 3.11], 0.6724		0.72 [0.21, 2.45], 0.6000	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.04 [-0.25, 0.16], 0.6793		-0.03 [-0.16, 0.09], 0.6132	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1068		0.1759		0.1507	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	6/23 (26.1)	8/48 (16.7)	0/16 (0.0)	11/84 (13.1)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.09, 1.15], 0.0814		5.50 [0.33, 90.61], 0.2331		0.85 [0.34, 2.13], 0.7312	
OR [95%-CI]; p-value	0.26 [0.06, 1.16], 0.0643		6.40 [0.35, 118.11], 0.1578		0.83 [0.28, 2.43], 0.7321	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.02], 0.0832		0.14 [0.00, 0.27], 0.0461		-0.02 [-0.16, 0.11], 0.7382	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	1/22 (4.5)	4/37 (10.8)	2/23 (8.7)	12/79 (15.2)	3/45 (6.7)
RR [95%-CI]; p-value	4.19 [0.56, 31.40], 0.1632		1.24 [0.25, 6.25], 0.7917		2.28 [0.68, 7.65], 0.1826	
OR [95%-CI]; p-value	4.94 [0.58, 42.37], 0.1129		1.27 [0.21, 7.57], 0.7906		2.51 [0.67, 9.41], 0.1617	
RD [95%-CI]; p-value	0.15 [-0.00, 0.29], 0.0536		0.02 [-0.13, 0.17], 0.7858		0.09 [-0.02, 0.19], 0.1205	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	3/17 (17.6)	1/34 (2.9)	3/21 (14.3)	5/71 (7.0)	6/38 (15.8)
RR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4872		0.21 [0.02, 1.85], 0.1585		0.45 [0.15, 1.37], 0.1575	
OR [95%-CI]; p-value	0.57 [0.11, 2.86], 0.4873		0.18 [0.02, 1.88], 0.1155		0.40 [0.11, 1.42], 0.1485	
RD [95%-CI]; p-value	-0.07 [-0.28, 0.14], 0.5175		-0.11 [-0.27, 0.05], 0.1648		-0.09 [-0.22, 0.04], 0.1883	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3647		0.8073		0.3635	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	5/23 (21.7)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	7/39 (17.9)
RR [95%-CI]; p-value	0.26 [0.05, 1.21], 0.0853		0.83 [0.18, 3.88], 0.8164		0.46 [0.17, 1.23], 0.1235	
OR [95%-CI]; p-value	0.21 [0.04, 1.20], 0.0608		0.81 [0.14, 4.67], 0.8171		0.42 [0.13, 1.28], 0.1182	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0855		-0.02 [-0.20, 0.16], 0.8241		-0.10 [-0.23, 0.04], 0.1601	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	1/22 (4.5)	3/37 (8.1)	1/23 (4.3)	6/79 (7.6)	2/45 (4.4)
RR [95%-CI]; p-value	1.57 [0.17, 14.23], 0.6877		1.86 [0.21, 16.87], 0.5792		1.71 [0.36, 8.11], 0.5002	
OR [95%-CI]; p-value	1.62 [0.16, 16.51], 0.6835		1.94 [0.19, 19.87], 0.5702		1.77 [0.34, 9.15], 0.4923	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6629		0.04 [-0.08, 0.16], 0.5430		0.03 [-0.05, 0.12], 0.4617	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	2/17 (11.8)	4/34 (11.8)	3/21 (14.3)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.23 [0.02, 2.36], 0.2161		0.82 [0.20, 3.32], 0.7850		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.21 [0.02, 2.48], 0.1769		0.80 [0.16, 3.99], 0.7852		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2724		-0.03 [-0.21, 0.16], 0.7891		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.9915		0.2242		0.2183	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.85 [0.21, 3.46], 0.8227		0.33 [0.02, 5.03], 0.4275		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.83 [0.17, 4.12], 0.8229		0.32 [0.02, 5.42], 0.4068		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.15], 0.8254		-0.04 [-0.17, 0.08], 0.5146		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	3/37 (8.1)	0/23 (0.0)	9/79 (11.4)	4/45 (8.9)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		3.81 [0.20, 72.73], 0.3739		1.28 [0.42, 3.93], 0.6640	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		4.06 [0.19, 84.88], 0.3315		1.32 [0.38, 4.55], 0.6617	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.06 [-0.05, 0.17], 0.2668		0.03 [-0.08, 0.13], 0.6518	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	2/34 (5.9)	6/21 (28.6)	4/71 (5.6)	7/38 (18.4)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.21 [0.05, 0.93], 0.0396		0.31 [0.10, 0.98], 0.0460	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.16 [0.03, 0.87], 0.0204		0.26 [0.07, 0.97], 0.0347	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.23 [-0.44, -0.02], 0.0332		-0.13 [-0.26, 0.01], 0.0622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.4.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9802		0.8567		0.7960	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	6/23 (26.1)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	6/39 (15.4)
RR [95%-CI]; p-value	0.21 [0.05, 0.97], 0.0450		1.37 [0.07, 28.98], 0.8378		0.31 [0.09, 1.03], 0.0568	
OR [95%-CI]; p-value	0.17 [0.03, 0.91], 0.0247		1.39 [0.06, 32.49], 0.8366		0.28 [0.07, 1.04], 0.0449	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.01], 0.0385		0.01 [-0.09, 0.11], 0.8241		-0.11 [-0.23, 0.02], 0.0880	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	1/22 (4.5)	1/37 (2.7)	0/23 (0.0)	1/79 (1.3)	1/45 (2.2)
RR [95%-CI]; p-value	0.26 [0.01, 7.42], 0.4298		1.27 [0.04, 36.39], 0.8889		0.57 [0.04, 8.89], 0.6881	
OR [95%-CI]; p-value	0.25 [0.01, 7.76], 0.3947		1.28 [0.04, 39.64], 0.8885		0.56 [0.03, 9.24], 0.6844	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.06], 0.4771		0.01 [-0.07, 0.08], 0.8856		-0.01 [-0.06, 0.04], 0.7056	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	5/17 (29.4)	3/34 (8.8)	0/21 (0.0)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.18 [0.04, 0.85], 0.0306		3.79 [0.20, 72.11], 0.3748		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.14 [0.02, 0.80], 0.0147		4.06 [0.19, 85.37], 0.3320		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.24 [-0.47, -0.01], 0.0395		0.06 [-0.05, 0.18], 0.2667		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_4_m_pt_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.2234		0.9985		0.3397	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	2/23 (8.7)	2/48 (4.2)	1/16 (6.3)	3/84 (3.6)	3/39 (7.7)
RR [95%-CI]; p-value	0.32 [0.03, 3.33], 0.3397		0.67 [0.06, 6.87], 0.7334		0.46 [0.10, 2.20], 0.3334	
OR [95%-CI]; p-value	0.30 [0.03, 3.51], 0.3129		0.65 [0.06, 7.71], 0.7328		0.44 [0.09, 2.31], 0.3235	
RD [95%-CI]; p-value	-0.06 [-0.19, 0.07], 0.3613		-0.02 [-0.15, 0.11], 0.7560		-0.04 [-0.13, 0.05], 0.3829	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	2/42 (4.8)	0/22 (0.0)	1/37 (2.7)	1/23 (4.3)	3/79 (3.8)	1/45 (2.2)
RR [95%-CI]; p-value	2.14 [0.10, 45.54], 0.6250		0.62 [0.04, 9.46], 0.7322		1.71 [0.18, 15.95], 0.6382	
OR [95%-CI]; p-value	2.20 [0.09, 50.95], 0.6145		0.61 [0.04, 10.27], 0.7300		1.74 [0.18, 17.21], 0.6331	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5744		-0.02 [-0.11, 0.08], 0.7431		0.02 [-0.04, 0.08], 0.6084	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	8/37 (21.6)	0/17 (0.0)	3/34 (8.8)	3/21 (14.3)	11/71 (15.5)	3/38 (7.9)
RR [95%-CI]; p-value	7.57 [0.46, 124.44], 0.1566		0.62 [0.14, 2.78], 0.5303		1.96 [0.58, 6.61], 0.2765	
OR [95%-CI]; p-value	9.38 [0.51, 173.76], 0.0746		0.58 [0.11, 3.19], 0.5279		2.14 [0.56, 8.19], 0.2585	
RD [95%-CI]; p-value	0.19 [0.03, 0.34], 0.0169		-0.05 [-0.23, 0.12], 0.5463		0.08 [-0.04, 0.20], 0.2151	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	NA		NA		NA	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	0/48 (0.0)	0/16 (0.0)	0/84 (0.0)	0/39 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	0/79 (0.0)	0/45 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	0/34 (0.0)	0/21 (0.0)	1/71 (1.4)	0/38 (0.0)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		NA		1.08 [0.04, 31.60], 0.9624	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		NA		1.09 [0.04, 33.11], 0.9624	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		NA		0.00 [-0.04, 0.05], 0.9619	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2505		0.9985		0.3831	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	2/23 (8.7)	2/48 (4.2)	1/16 (6.3)	3/84 (3.6)	3/39 (7.7)
RR [95%-CI]; p-value	0.32 [0.03, 3.33], 0.3397		0.67 [0.06, 6.87], 0.7334		0.46 [0.10, 2.20], 0.3334	
OR [95%-CI]; p-value	0.30 [0.03, 3.51], 0.3129		0.65 [0.06, 7.71], 0.7328		0.44 [0.09, 2.31], 0.3235	
RD [95%-CI]; p-value	-0.06 [-0.19, 0.07], 0.3613		-0.02 [-0.15, 0.11], 0.7560		-0.04 [-0.13, 0.05], 0.3829	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	2/42 (4.8)	0/22 (0.0)	1/37 (2.7)	1/23 (4.3)	3/79 (3.8)	1/45 (2.2)
RR [95%-CI]; p-value	2.14 [0.10, 45.54], 0.6250		0.62 [0.04, 9.46], 0.7322		1.71 [0.18, 15.95], 0.6382	
OR [95%-CI]; p-value	2.20 [0.09, 50.95], 0.6145		0.61 [0.04, 10.27], 0.7300		1.74 [0.18, 17.21], 0.6331	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5744		-0.02 [-0.11, 0.08], 0.7431		0.02 [-0.04, 0.08], 0.6084	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	0/17 (0.0)	3/34 (8.8)	3/21 (14.3)	10/71 (14.1)	3/38 (7.9)
RR [95%-CI]; p-value	6.62 [0.40, 110.22], 0.1877		0.62 [0.14, 2.78], 0.5303		1.78 [0.52, 6.10], 0.3558	
OR [95%-CI]; p-value	7.93 [0.42, 148.59], 0.1080		0.58 [0.11, 3.19], 0.5279		1.91 [0.49, 7.42], 0.3420	
RD [95%-CI]; p-value	0.16 [0.01, 0.31], 0.0339		-0.05 [-0.23, 0.12], 0.5463		0.06 [-0.06, 0.18], 0.3034	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8095		NA		0.5904	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	1/23 (4.3)	0/48 (0.0)	0/16 (0.0)	1/84 (1.2)	1/39 (2.6)
RR [95%-CI]; p-value	0.64 [0.04, 9.72], 0.7470		NA		0.46 [0.03, 7.23], 0.5839	
OR [95%-CI]; p-value	0.63 [0.04, 10.57], 0.7452		NA		0.46 [0.03, 7.52], 0.5751	
RD [95%-CI]; p-value	-0.02 [-0.11, 0.08], 0.7563		NA		-0.01 [-0.07, 0.04], 0.6230	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	2/42 (4.8)	0/22 (0.0)	1/37 (2.7)	0/23 (0.0)	3/79 (3.8)	0/45 (0.0)
RR [95%-CI]; p-value	2.14 [0.10, 45.54], 0.6250		1.27 [0.04, 36.39], 0.8889		3.46 [0.18, 67.47], 0.4134	
OR [95%-CI]; p-value	2.20 [0.09, 50.95], 0.6145		1.28 [0.04, 39.64], 0.8885		3.55 [0.17, 72.54], 0.3804	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5744		0.01 [-0.07, 0.08], 0.8856		0.03 [-0.02, 0.08], 0.3082	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	0/17 (0.0)	0/34 (0.0)	0/21 (0.0)	2/71 (2.8)	0/38 (0.0)
RR [95%-CI]; p-value	1.89 [0.09, 39.80], 0.6817		NA		2.17 [0.10, 46.91], 0.6215	
OR [95%-CI]; p-value	1.94 [0.08, 45.46], 0.6746		NA		2.20 [0.10, 50.10], 0.6116	
RD [95%-CI]; p-value	0.03 [-0.08, 0.13], 0.6400		NA		0.02 [-0.04, 0.07], 0.5711	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.1280		0.4295		0.0679	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	4/23 (17.4)	3/48 (6.3)	1/16 (6.3)	3/84 (3.6)	5/39 (12.8)
RR [95%-CI]; p-value	0.08 [0.00, 1.42], 0.0852		1.00 [0.11, 8.95], 1.0000		0.28 [0.07, 1.11], 0.0695	
OR [95%-CI]; p-value	0.07 [0.00, 1.31], 0.0228		1.00 [0.10, 10.35], 1.0000		0.25 [0.06, 1.11], 0.0529	
RD [95%-CI]; p-value	-0.16 [-0.32, -0.00], 0.0489		0.00 [-0.14, 0.14], 1.0000		-0.09 [-0.20, 0.02], 0.1061	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	7/42 (16.7)	2/22 (9.1)	4/37 (10.8)	1/23 (4.3)	11/79 (13.9)	3/45 (6.7)
RR [95%-CI]; p-value	1.83 [0.42, 8.09], 0.4235		2.49 [0.30, 20.89], 0.4016		2.09 [0.61, 7.10], 0.2379	
OR [95%-CI]; p-value	2.00 [0.38, 10.57], 0.4076		2.67 [0.28, 25.47], 0.3785		2.26 [0.60, 8.59], 0.2195	
RD [95%-CI]; p-value	0.08 [-0.09, 0.24], 0.3674		0.06 [-0.07, 0.19], 0.3307		0.07 [-0.03, 0.18], 0.1778	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	3/37 (8.1)	3/17 (17.6)	2/34 (5.9)	3/21 (14.3)	5/71 (7.0)	6/38 (15.8)
RR [95%-CI]; p-value	0.46 [0.10, 2.05], 0.3075		0.41 [0.07, 2.26], 0.3076		0.45 [0.15, 1.37], 0.1575	
OR [95%-CI]; p-value	0.41 [0.07, 2.29], 0.3002		0.38 [0.06, 2.46], 0.2922		0.40 [0.11, 1.42], 0.1485	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3533		-0.08 [-0.25, 0.09], 0.3306		-0.09 [-0.22, 0.04], 0.1883	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	NA		0.8390		0.9345	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	1/48 (2.1)	0/16 (0.0)	1/84 (1.2)	0/39 (0.0)
RR [95%-CI]; p-value	NA		0.69 [0.02, 19.56], 0.8264		0.94 [0.03, 27.45], 0.9716	
OR [95%-CI]; p-value	NA		0.68 [0.02, 21.27], 0.8257		0.94 [0.03, 28.61], 0.9716	
RD [95%-CI]; p-value	NA		-0.01 [-0.10, 0.08], 0.8402		-0.00 [-0.04, 0.04], 0.9719	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	1/37 (2.7)	0/23 (0.0)	1/79 (1.3)	0/45 (0.0)
RR [95%-CI]; p-value	NA		1.27 [0.04, 36.39], 0.8889		1.15 [0.04, 33.67], 0.9346	
OR [95%-CI]; p-value	NA		1.28 [0.04, 39.64], 0.8885		1.15 [0.04, 35.08], 0.9345	
RD [95%-CI]; p-value	NA		0.01 [-0.07, 0.08], 0.8856		0.00 [-0.04, 0.04], 0.9332	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	0/34 (0.0)	1/21 (4.8)	1/71 (1.4)	1/38 (2.6)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		0.30 [0.01, 8.68], 0.4866		0.54 [0.03, 8.32], 0.6552	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		0.29 [0.01, 9.17], 0.4605		0.53 [0.03, 8.69], 0.6502	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		-0.03 [-0.13, 0.07], 0.5138		-0.01 [-0.07, 0.05], 0.6784	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.0969		0.4282		0.0336	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	4/23 (17.4)	2/48 (4.2)	1/16 (6.3)	2/84 (2.4)	5/39 (12.8)
RR [95%-CI]; p-value	0.08 [0.00, 1.42], 0.0852		0.67 [0.06, 6.87], 0.7334		0.19 [0.04, 0.92], 0.0386	
OR [95%-CI]; p-value	0.07 [0.00, 1.31], 0.0228		0.65 [0.06, 7.71], 0.7328		0.17 [0.03, 0.90], 0.0200	
RD [95%-CI]; p-value	-0.16 [-0.32, -0.00], 0.0489		-0.02 [-0.15, 0.11], 0.7560		-0.10 [-0.21, 0.01], 0.0626	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	7/42 (16.7)	2/22 (9.1)	4/37 (10.8)	1/23 (4.3)	11/79 (13.9)	3/45 (6.7)
RR [95%-CI]; p-value	1.83 [0.42, 8.09], 0.4235		2.49 [0.30, 20.89], 0.4016		2.09 [0.61, 7.10], 0.2379	
OR [95%-CI]; p-value	2.00 [0.38, 10.57], 0.4076		2.67 [0.28, 25.47], 0.3785		2.26 [0.60, 8.59], 0.2195	
RD [95%-CI]; p-value	0.08 [-0.09, 0.24], 0.3674		0.06 [-0.07, 0.19], 0.3307		0.07 [-0.03, 0.18], 0.1778	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	3/17 (17.6)	2/34 (5.9)	3/21 (14.3)	4/71 (5.6)	6/38 (15.8)
RR [95%-CI]; p-value	0.31 [0.06, 1.67], 0.1712		0.41 [0.07, 2.26], 0.3076		0.36 [0.11, 1.19], 0.0929	
OR [95%-CI]; p-value	0.27 [0.04, 1.77], 0.1495		0.38 [0.06, 2.46], 0.2922		0.32 [0.08, 1.21], 0.0801	
RD [95%-CI]; p-value	-0.12 [-0.32, 0.07], 0.2193		-0.08 [-0.25, 0.09], 0.3306		-0.10 [-0.23, 0.03], 0.1192	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.7749		0.7744		0.5691	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	2/48 (4.2)	0/16 (0.0)	2/84 (2.4)	0/39 (0.0)
RR [95%-CI]; p-value	NA		1.37 [0.07, 28.98], 0.8378		1.88 [0.09, 40.76], 0.6873	
OR [95%-CI]; p-value	NA		1.39 [0.06, 32.49], 0.8366		1.90 [0.08, 43.18], 0.6815	
RD [95%-CI]; p-value	NA		0.01 [-0.09, 0.11], 0.8241		0.01 [-0.04, 0.06], 0.6470	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	0/22 (0.0)	1/37 (2.7)	0/23 (0.0)	4/79 (5.1)	0/45 (0.0)
RR [95%-CI]; p-value	3.21 [0.17, 61.40], 0.4379		1.27 [0.04, 36.39], 0.8889		4.61 [0.25, 85.19], 0.3047	
OR [95%-CI]; p-value	3.38 [0.16, 70.70], 0.4057		1.28 [0.04, 39.64], 0.8885		4.80 [0.25, 92.92], 0.2538	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3294		0.01 [-0.07, 0.08], 0.8856		0.04 [-0.02, 0.10], 0.1732	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	0/34 (0.0)	1/21 (4.8)	1/71 (1.4)	1/38 (2.6)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		0.30 [0.01, 8.68], 0.4866		0.54 [0.03, 8.32], 0.6552	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		0.29 [0.01, 9.17], 0.4605		0.53 [0.03, 8.69], 0.6502	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		-0.03 [-0.13, 0.07], 0.5138		-0.01 [-0.07, 0.05], 0.6784	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.6.s6.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.9209		0.9261		0.8527	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	6/36 (16.7)	7/23 (30.4)	10/48 (20.8)	2/16 (12.5)	16/84 (19.0)	9/39 (23.1)
RR [95%-CI]; p-value	0.55 [0.21, 1.43], 0.2173		1.67 [0.41, 6.82], 0.4773		0.83 [0.40, 1.70], 0.6029	
OR [95%-CI]; p-value	0.46 [0.13, 1.59], 0.2133		1.84 [0.36, 9.47], 0.4595		0.78 [0.31, 1.97], 0.6053	
RD [95%-CI]; p-value	-0.14 [-0.36, 0.09], 0.2284		0.08 [-0.12, 0.28], 0.4109		-0.04 [-0.20, 0.12], 0.6141	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	4/22 (18.2)	4/37 (10.8)	2/23 (8.7)	7/79 (8.9)	6/45 (13.3)
RR [95%-CI]; p-value	0.39 [0.10, 1.60], 0.1925		1.24 [0.25, 6.25], 0.7917		0.66 [0.24, 1.86], 0.4355	
OR [95%-CI]; p-value	0.35 [0.07, 1.71], 0.1790		1.27 [0.21, 7.57], 0.7906		0.63 [0.20, 2.01], 0.4344	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2268		0.02 [-0.13, 0.17], 0.7858		-0.04 [-0.16, 0.07], 0.4554	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	6/17 (35.3)	9/34 (26.5)	3/21 (14.3)	16/71 (22.5)	9/38 (23.7)
RR [95%-CI]; p-value	0.54 [0.21, 1.35], 0.1873		1.85 [0.56, 6.08], 0.3089		0.95 [0.47, 1.95], 0.8916	
OR [95%-CI]; p-value	0.43 [0.12, 1.56], 0.1911		2.16 [0.51, 9.12], 0.2878		0.94 [0.37, 2.38], 0.8918	
RD [95%-CI]; p-value	-0.16 [-0.42, 0.10], 0.2168		0.12 [-0.09, 0.33], 0.2570		-0.01 [-0.18, 0.15], 0.8924	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_6_m_pt_adr_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.2423		0.1208		0.0071	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	8/13 (61.5)	5/5 (100.0)	12/27 (44.4)	3/4 (75.0)	20/40 (50.0)	8/9 (88.9)
RR [95%-CI]; p-value	0.68 [0.41, 1.12], 0.1296		0.59 [0.29, 1.20], 0.1461		0.56 [0.38, 0.83], 0.0035	
OR [95%-CI]; p-value	0.16 [0.01, 3.60], 0.2065		0.27 [0.02, 2.90], 0.2538		0.13 [0.01, 1.09], 0.0332	
RD [95%-CI]; p-value	-0.29 [-0.65, 0.06], 0.1072		-0.31 [-0.77, 0.16], 0.1967		-0.39 [-0.65, -0.13], 0.0030	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	75/102 (73.5)	45/57 (78.9)	60/92 (65.2)	34/56 (60.7)	135/194 (69.6)	79/113 (69.9)
RR [95%-CI]; p-value	0.93 [0.78, 1.11], 0.4326		1.07 [0.83, 1.39], 0.5870		1.00 [0.85, 1.16], 0.9524	
OR [95%-CI]; p-value	0.74 [0.34, 1.61], 0.4464		1.21 [0.61, 2.41], 0.5810		0.98 [0.59, 1.63], 0.9525	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.08], 0.4354		0.05 [-0.12, 0.21], 0.5829		-0.00 [-0.11, 0.10], 0.9525	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.7694		0.3351		0.8970	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	2/40 (5.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		0.67 [0.04, 12.53], 0.7865		0.95 [0.05, 19.41], 0.9734	
OR [95%-CI]; p-value	NA		0.64 [0.02, 16.90], 0.7879		0.95 [0.04, 22.85], 0.9734	
RD [95%-CI]; p-value	NA		-0.04 [-0.34, 0.27], 0.8129		-0.00 [-0.16, 0.15], 0.9738	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	13/102 (12.7)	10/57 (17.5)	11/92 (12.0)	2/56 (3.6)	24/194 (12.4)	12/113 (10.6)
RR [95%-CI]; p-value	0.73 [0.34, 1.55], 0.4087		3.35 [0.77, 14.55], 0.1071		1.16 [0.61, 2.24], 0.6468	
OR [95%-CI]; p-value	0.69 [0.28, 1.68], 0.4094		3.67 [0.78, 17.20], 0.0805		1.19 [0.57, 2.48], 0.6455	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.07], 0.4256		0.08 [0.00, 0.17], 0.0456		0.02 [-0.06, 0.09], 0.6395	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.0314		0.6968		0.0518	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		NA		0.06 [0.00, 1.13], 0.0601	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		NA		0.04 [0.00, 1.07], 0.0093	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		NA		-0.21 [-0.48, 0.06], 0.1329	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	12/102 (11.8)	2/57 (3.5)	3/92 (3.3)	5/56 (8.9)	15/194 (7.7)	7/113 (6.2)
RR [95%-CI]; p-value	3.35 [0.78, 14.46], 0.1047		0.37 [0.09, 1.47], 0.1562		1.25 [0.52, 2.97], 0.6161	
OR [95%-CI]; p-value	3.67 [0.79, 17.00], 0.0781		0.34 [0.08, 1.50], 0.1392		1.27 [0.50, 3.21], 0.6145	
RD [95%-CI]; p-value	0.08 [0.00, 0.16], 0.0397		-0.06 [-0.14, 0.03], 0.1810		0.02 [-0.04, 0.07], 0.6047	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.0993		0.5270		0.0650	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	2/5 (40.0)	3/27 (11.1)	1/4 (25.0)	4/40 (10.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.19 [0.02, 1.68], 0.1360		0.44 [0.06, 3.30], 0.4279		0.30 [0.08, 1.11], 0.0718	
OR [95%-CI]; p-value	0.13 [0.01, 1.89], 0.0995		0.38 [0.03, 4.86], 0.4393		0.22 [0.04, 1.25], 0.0707	
RD [95%-CI]; p-value	-0.32 [-0.78, 0.13], 0.1623		-0.14 [-0.58, 0.30], 0.5367		-0.23 [-0.56, 0.09], 0.1552	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	19/102 (18.6)	8/57 (14.0)	9/92 (9.8)	6/56 (10.7)	28/194 (14.4)	14/113 (12.4)
RR [95%-CI]; p-value	1.33 [0.62, 2.84], 0.4653		0.91 [0.34, 2.43], 0.8554		1.16 [0.64, 2.12], 0.6169	
OR [95%-CI]; p-value	1.40 [0.57, 3.44], 0.4595		0.90 [0.30, 2.69], 0.8555		1.19 [0.60, 2.37], 0.6153	
RD [95%-CI]; p-value	0.05 [-0.07, 0.16], 0.4442		-0.01 [-0.11, 0.09], 0.8568		0.02 [-0.06, 0.10], 0.6091	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.5256		0.1360		0.2500	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	8/102 (7.8)	3/57 (5.3)	5/92 (5.4)	0/56 (0.0)	13/194 (6.7)	3/113 (2.7)
RR [95%-CI]; p-value	1.49 [0.41, 5.40], 0.5434		6.14 [0.34, 110.30], 0.2181		2.52 [0.73, 8.67], 0.1413	
OR [95%-CI]; p-value	1.53 [0.39, 6.02], 0.5387		6.44 [0.34, 120.12], 0.1541		2.63 [0.73, 9.45], 0.1240	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.5167		0.05 [-0.01, 0.10], 0.0886		0.04 [-0.01, 0.09], 0.0848	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8948		NA		0.7070	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	1/102 (1.0)	1/57 (1.8)	0/92 (0.0)	0/56 (0.0)	1/194 (0.5)	1/113 (0.9)
RR [95%-CI]; p-value	0.56 [0.04, 8.77], 0.6786		NA		0.58 [0.04, 9.22], 0.7013	
OR [95%-CI]; p-value	0.55 [0.03, 9.04], 0.6745		NA		0.58 [0.04, 9.37], 0.6979	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.6979		NA		-0.00 [-0.02, 0.02], 0.7172	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.6685		NA		0.5263	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	1/5 (20.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	0.19 [0.01, 4.71], 0.3071		NA		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	0.15 [0.00, 5.49], 0.2541		NA		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	-0.16 [-0.53, 0.20], 0.3813		NA		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	0/102 (0.0)	0/57 (0.0)	0/92 (0.0)	0/56 (0.0)	0/194 (0.0)	0/113 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.2456		0.0222		0.0015	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	7/13 (53.8)	5/5 (100.0)	9/27 (33.3)	3/4 (75.0)	16/40 (40.0)	8/9 (88.9)
RR [95%-CI]; p-value	0.59 [0.34, 1.05], 0.0710		0.44 [0.20, 0.97], 0.0410		0.45 [0.29, 0.70], 0.0004	
OR [95%-CI]; p-value	0.12 [0.01, 2.60], 0.1269		0.17 [0.02, 1.84], 0.1103		0.08 [0.01, 0.73], 0.0080	
RD [95%-CI]; p-value	-0.37 [-0.73, -0.01], 0.0449		-0.42 [-0.88, 0.04], 0.0759		-0.49 [-0.74, -0.23], 0.0002	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	61/102 (59.8)	40/57 (70.2)	51/92 (55.4)	26/56 (46.4)	112/194 (57.7)	66/113 (58.4)
RR [95%-CI]; p-value	0.85 [0.68, 1.08], 0.1772		1.19 [0.85, 1.67], 0.3007		0.99 [0.81, 1.20], 0.9078	
OR [95%-CI]; p-value	0.63 [0.32, 1.26], 0.1926		1.44 [0.74, 2.80], 0.2875		0.97 [0.61, 1.56], 0.9080	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.05], 0.1816		0.09 [-0.08, 0.26], 0.2860		-0.01 [-0.12, 0.11], 0.9079	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.6168		0.9648		0.7795	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	8/27 (29.6)	1/4 (25.0)	11/40 (27.5)	3/9 (33.3)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		1.19 [0.20, 7.13], 0.8528		0.83 [0.29, 2.36], 0.7201	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		1.26 [0.11, 14.05], 0.8490		0.76 [0.16, 3.57], 0.7263	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		0.05 [-0.41, 0.50], 0.8429		-0.06 [-0.40, 0.28], 0.7349	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	35/102 (34.3)	23/57 (40.4)	28/92 (30.4)	15/56 (26.8)	63/194 (32.5)	38/113 (33.6)
RR [95%-CI]; p-value	0.85 [0.56, 1.29], 0.4434		1.14 [0.67, 1.93], 0.6379		0.97 [0.69, 1.34], 0.8352	
OR [95%-CI]; p-value	0.77 [0.40, 1.51], 0.4482		1.20 [0.57, 2.51], 0.6353		0.95 [0.58, 1.55], 0.8356	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.10], 0.4516		0.04 [-0.11, 0.19], 0.6319		-0.01 [-0.12, 0.10], 0.8359	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.0314		0.6968		0.0518	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		NA		0.06 [0.00, 1.13], 0.0601	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		NA		0.04 [0.00, 1.07], 0.0093	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		NA		-0.21 [-0.48, 0.06], 0.1329	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	12/102 (11.8)	2/57 (3.5)	3/92 (3.3)	5/56 (8.9)	15/194 (7.7)	7/113 (6.2)
RR [95%-CI]; p-value	3.35 [0.78, 14.46], 0.1047		0.37 [0.09, 1.47], 0.1562		1.25 [0.52, 2.97], 0.6161	
OR [95%-CI]; p-value	3.67 [0.79, 17.00], 0.0781		0.34 [0.08, 1.50], 0.1392		1.27 [0.50, 3.21], 0.6145	
RD [95%-CI]; p-value	0.08 [0.00, 0.16], 0.0397		-0.06 [-0.14, 0.03], 0.1810		0.02 [-0.04, 0.07], 0.6047	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.2188		0.3548		0.0919	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	1/27 (3.7)	0/4 (0.0)	1/40 (2.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.33 [0.01, 8.55], 0.5069		0.11 [0.01, 1.11], 0.0614	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.31 [0.01, 10.76], 0.4945		0.09 [0.01, 1.13], 0.0258	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.07 [-0.37, 0.22], 0.6273		-0.20 [-0.47, 0.08], 0.1612	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	8/102 (7.8)	7/57 (12.3)	6/92 (6.5)	2/56 (3.6)	14/194 (7.2)	9/113 (8.0)
RR [95%-CI]; p-value	0.64 [0.24, 1.67], 0.3606		1.83 [0.38, 8.74], 0.4509		0.91 [0.41, 2.03], 0.8101	
OR [95%-CI]; p-value	0.61 [0.21, 1.77], 0.3586		1.88 [0.37, 9.67], 0.4414		0.90 [0.38, 2.15], 0.8102	
RD [95%-CI]; p-value	-0.04 [-0.14, 0.06], 0.3840		0.03 [-0.04, 0.10], 0.4091		-0.01 [-0.07, 0.05], 0.8124	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6898		0.4224		0.7715	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	6/27 (22.2)	1/4 (25.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.89 [0.14, 5.59], 0.9001		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.86 [0.07, 9.82], 0.9013		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.03 [-0.48, 0.42], 0.9042		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	20/102 (19.6)	17/57 (29.8)	17/92 (18.5)	5/56 (8.9)	37/194 (19.1)	22/113 (19.5)
RR [95%-CI]; p-value	0.66 [0.38, 1.15], 0.1417		2.07 [0.81, 5.30], 0.1294		0.98 [0.61, 1.57], 0.9321	
OR [95%-CI]; p-value	0.57 [0.27, 1.21], 0.1437		2.31 [0.80, 6.66], 0.1132		0.97 [0.54, 1.75], 0.9322	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.04], 0.1572		0.10 [-0.01, 0.20], 0.0858		-0.00 [-0.10, 0.09], 0.9323	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.2048		0.2380		0.0520	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	2/27 (7.4)	1/4 (25.0)	2/40 (5.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.30 [0.03, 2.57], 0.2694		0.15 [0.03, 0.77], 0.0231	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.24 [0.02, 3.51], 0.2667		0.11 [0.01, 0.77], 0.0112	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.18 [-0.61, 0.26], 0.4287		-0.28 [-0.60, 0.03], 0.0782	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	15/102 (14.7)	13/57 (22.8)	12/92 (13.0)	6/56 (10.7)	27/194 (13.9)	19/113 (16.8)
RR [95%-CI]; p-value	0.64 [0.33, 1.26], 0.1981		1.22 [0.48, 3.06], 0.6758		0.83 [0.48, 1.42], 0.4919	
OR [95%-CI]; p-value	0.58 [0.26, 1.33], 0.1984		1.25 [0.44, 3.54], 0.6742		0.80 [0.42, 1.52], 0.4928	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2177		0.02 [-0.08, 0.13], 0.6676		-0.03 [-0.11, 0.06], 0.5013	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.4561		0.7089		0.3445	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	5/27 (18.5)	1/4 (25.0)	8/40 (20.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		0.74 [0.11, 4.82], 0.7535		0.60 [0.20, 1.83], 0.3682	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		0.68 [0.06, 8.00], 0.7594		0.50 [0.10, 2.45], 0.3864	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		-0.06 [-0.51, 0.38], 0.7772		-0.13 [-0.47, 0.20], 0.4312	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	28/102 (27.5)	15/57 (26.3)	23/92 (25.0)	13/56 (23.2)	51/194 (26.3)	28/113 (24.8)
RR [95%-CI]; p-value	1.04 [0.61, 1.78], 0.8775		1.08 [0.59, 1.95], 0.8066		1.06 [0.71, 1.58], 0.7711	
OR [95%-CI]; p-value	1.06 [0.51, 2.20], 0.8772		1.10 [0.51, 2.40], 0.8060		1.08 [0.64, 1.85], 0.7704	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8767		0.02 [-0.12, 0.16], 0.8048		0.02 [-0.09, 0.12], 0.7692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.7399		0.7681		0.9759	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	4/27 (14.8)	0/4 (0.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		1.33 [0.08, 21.18], 0.8384		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		1.39 [0.06, 31.69], 0.8353		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		0.04 [-0.28, 0.36], 0.8204		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	8/57 (14.0)	7/92 (7.6)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.77 [0.33, 1.80], 0.5440		0.85 [0.28, 2.56], 0.7753		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.74 [0.28, 1.96], 0.5445		0.84 [0.25, 2.79], 0.7754		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.5568		-0.01 [-0.11, 0.08], 0.7792		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0212		0.0518		0.0003	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	5/5 (100.0)	3/27 (11.1)	2/4 (50.0)	4/40 (10.0)	7/9 (77.8)
RR [95%-CI]; p-value	0.08 [0.01, 0.57], 0.0109		0.22 [0.05, 0.95], 0.0419		0.13 [0.05, 0.35], <0.0001	
OR [95%-CI]; p-value	0.01 [0.00, 0.29], 0.0005		0.13 [0.01, 1.24], 0.0484		0.03 [0.00, 0.21], <0.0001	
RD [95%-CI]; p-value	-0.83 [-1.00, -0.55], <0.0001		-0.39 [-0.89, 0.12], 0.1305		-0.68 [-0.96, -0.39], <0.0001	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	22/102 (21.6)	14/57 (24.6)	18/92 (19.6)	10/56 (17.9)	40/194 (20.6)	24/113 (21.2)
RR [95%-CI]; p-value	0.88 [0.49, 1.58], 0.6641		1.10 [0.55, 2.20], 0.7976		0.97 [0.62, 1.52], 0.8972	
OR [95%-CI]; p-value	0.84 [0.39, 1.82], 0.6654		1.12 [0.48, 2.63], 0.7969		0.96 [0.55, 1.70], 0.8973	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6693		0.02 [-0.11, 0.15], 0.7952		-0.01 [-0.10, 0.09], 0.8976	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.6775		0.8376		0.8733	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	3/27 (11.1)	0/4 (0.0)	5/40 (12.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		1.00 [0.06, 16.82], 1.0000		0.56 [0.13, 2.45], 0.4436	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		1.00 [0.04, 23.94], 1.0000		0.50 [0.08, 3.12], 0.4514	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		0.00 [-0.31, 0.31], 1.0000		-0.10 [-0.39, 0.19], 0.5116	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	18/102 (17.6)	18/57 (31.6)	17/92 (18.5)	14/56 (25.0)	35/194 (18.0)	32/113 (28.3)
RR [95%-CI]; p-value	0.56 [0.32, 0.99], 0.0444		0.74 [0.40, 1.38], 0.3428		0.64 [0.42, 0.97], 0.0352	
OR [95%-CI]; p-value	0.46 [0.22, 0.99], 0.0441		0.68 [0.30, 1.52], 0.3444		0.56 [0.32, 0.96], 0.0355	
RD [95%-CI]; p-value	-0.14 [-0.28, 0.00], 0.0537		-0.07 [-0.20, 0.07], 0.3557		-0.10 [-0.20, -0.00], 0.0422	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.4803		0.1299		0.0962	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	1/5 (20.0)	1/27 (3.7)	1/4 (25.0)	1/40 (2.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.19 [0.01, 4.71], 0.3071		0.15 [0.01, 1.93], 0.1446		0.11 [0.01, 1.11], 0.0614	
OR [95%-CI]; p-value	0.15 [0.00, 5.49], 0.2541		0.12 [0.01, 2.36], 0.1057		0.09 [0.01, 1.13], 0.0258	
RD [95%-CI]; p-value	-0.16 [-0.53, 0.20], 0.3813		-0.21 [-0.64, 0.22], 0.3320		-0.20 [-0.47, 0.08], 0.1612	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	10/57 (17.5)	12/92 (13.0)	6/56 (10.7)	23/194 (11.9)	16/113 (14.2)
RR [95%-CI]; p-value	0.61 [0.28, 1.36], 0.2289		1.22 [0.48, 3.06], 0.6758		0.84 [0.46, 1.52], 0.5582	
OR [95%-CI]; p-value	0.57 [0.23, 1.43], 0.2273		1.25 [0.44, 3.54], 0.6742		0.82 [0.41, 1.62], 0.5589	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.05], 0.2519		0.02 [-0.08, 0.13], 0.6676		-0.02 [-0.10, 0.06], 0.5664	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3333		0.0582		0.0439	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.07 [0.00, 1.84], 0.1116		0.04 [0.00, 0.68], 0.0262	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.06 [0.00, 2.03], 0.0419		0.03 [0.00, 0.56], 0.0007	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.23 [-0.66, 0.20], 0.2876		-0.32 [-0.63, -0.01], 0.0423	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	4/102 (3.9)	5/57 (8.8)	5/92 (5.4)	1/56 (1.8)	9/194 (4.6)	6/113 (5.3)
RR [95%-CI]; p-value	0.45 [0.13, 1.60], 0.2156		3.04 [0.36, 25.39], 0.3038		0.87 [0.32, 2.39], 0.7927	
OR [95%-CI]; p-value	0.42 [0.11, 1.65], 0.2044		3.16 [0.36, 27.78], 0.2750		0.87 [0.30, 2.50], 0.7927	
RD [95%-CI]; p-value	-0.05 [-0.13, 0.03], 0.2494		0.04 [-0.02, 0.09], 0.2165		-0.01 [-0.06, 0.04], 0.7960	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3645		0.4617		0.2116	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	4/27 (14.8)	1/4 (25.0)	6/40 (15.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		0.59 [0.09, 4.06], 0.5939		0.45 [0.14, 1.47], 0.1856	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		0.52 [0.04, 6.36], 0.6052		0.35 [0.07, 1.81], 0.1994	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		-0.10 [-0.55, 0.34], 0.6537		-0.18 [-0.51, 0.14], 0.2722	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	13/102 (12.7)	8/57 (14.0)	9/92 (9.8)	4/56 (7.1)	22/194 (11.3)	12/113 (10.6)
RR [95%-CI]; p-value	0.91 [0.40, 2.06], 0.8175		1.37 [0.44, 4.24], 0.5854		1.07 [0.55, 2.07], 0.8463	
OR [95%-CI]; p-value	0.89 [0.35, 2.31], 0.8178		1.41 [0.41, 4.81], 0.5822		1.08 [0.51, 2.27], 0.8461	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.10], 0.8198		0.03 [-0.06, 0.12], 0.5686		0.01 [-0.07, 0.08], 0.8450	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9887		0.0816		0.2511	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	NA		0.07 [0.00, 1.84], 0.1116		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	NA		0.06 [0.00, 2.03], 0.0419		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	NA		-0.23 [-0.66, 0.20], 0.2876		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	6/102 (5.9)	8/57 (14.0)	12/92 (13.0)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.42 [0.15, 1.15], 0.0908		1.46 [0.54, 3.93], 0.4525		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.38 [0.13, 1.17], 0.0819		1.53 [0.51, 4.60], 0.4464		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.08 [-0.18, 0.02], 0.1139		0.04 [-0.06, 0.14], 0.4271		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.6758		0.0604		0.1503	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	0/27 (0.0)	2/4 (50.0)	3/40 (7.5)	3/9 (33.3)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.04 [0.00, 0.67], 0.0259		0.23 [0.05, 0.94], 0.0406	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.02 [0.00, 0.56], 0.0009		0.16 [0.03, 1.00], 0.0327	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.48 [-0.97, 0.01], 0.0552		-0.26 [-0.58, 0.06], 0.1120	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	9/102 (8.8)	7/57 (12.3)	6/92 (6.5)	5/56 (8.9)	15/194 (7.7)	12/113 (10.6)
RR [95%-CI]; p-value	0.72 [0.28, 1.83], 0.4874		0.73 [0.23, 2.28], 0.5890		0.73 [0.35, 1.50], 0.3895	
OR [95%-CI]; p-value	0.69 [0.24, 1.97], 0.4871		0.71 [0.21, 2.45], 0.5882		0.71 [0.32, 1.57], 0.3889	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5041		-0.02 [-0.11, 0.07], 0.6007		-0.03 [-0.10, 0.04], 0.4060	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.3.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5249		0.1886		0.9615	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	2/40 (5.0)	1/9 (11.1)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.33 [0.01, 8.55], 0.5069		0.45 [0.05, 4.44], 0.4941	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.31 [0.01, 10.76], 0.4945		0.42 [0.03, 5.23], 0.4896	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.07 [-0.37, 0.22], 0.6273		-0.06 [-0.28, 0.16], 0.5795	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	3/102 (2.9)	11/57 (19.3)	5/92 (5.4)	0/56 (0.0)	8/194 (4.1)	11/113 (9.7)
RR [95%-CI]; p-value	0.15 [0.04, 0.52], 0.0028		6.14 [0.34, 110.30], 0.2181		0.42 [0.18, 1.02], 0.0559	
OR [95%-CI]; p-value	0.13 [0.03, 0.48], 0.0005		6.44 [0.34, 120.12], 0.1541		0.40 [0.16, 1.02], 0.0491	
RD [95%-CI]; p-value	-0.16 [-0.27, -0.06], 0.0029		0.05 [-0.01, 0.10], 0.0886		-0.06 [-0.12, 0.01], 0.0733	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_3_m_pt_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.3.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.7742		0.3548		0.3050	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	2/5 (40.0)	1/27 (3.7)	0/4 (0.0)	2/40 (5.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.19 [0.02, 1.68], 0.1360		0.33 [0.01, 8.55], 0.5069		0.23 [0.04, 1.39], 0.1085	
OR [95%-CI]; p-value	0.13 [0.01, 1.89], 0.0995		0.31 [0.01, 10.76], 0.4945		0.18 [0.02, 1.53], 0.0882	
RD [95%-CI]; p-value	-0.32 [-0.78, 0.13], 0.1623		-0.07 [-0.37, 0.22], 0.6273		-0.17 [-0.45, 0.11], 0.2278	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	3/102 (2.9)	6/57 (10.5)	6/92 (6.5)	2/56 (3.6)	9/194 (4.6)	8/113 (7.1)
RR [95%-CI]; p-value	0.28 [0.07, 1.08], 0.0636		1.83 [0.38, 8.74], 0.4509		0.66 [0.26, 1.65], 0.3698	
OR [95%-CI]; p-value	0.26 [0.06, 1.07], 0.0472		1.88 [0.37, 9.67], 0.4414		0.64 [0.24, 1.70], 0.3672	
RD [95%-CI]; p-value	-0.08 [-0.16, 0.01], 0.0844		0.03 [-0.04, 0.10], 0.4091		-0.02 [-0.08, 0.03], 0.3912	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_3_m_pt_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.3.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.7742		0.0855		0.0750	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	1/5 (20.0)	0/27 (0.0)	2/4 (50.0)	2/40 (5.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.77 [0.09, 6.72], 0.8125		0.04 [0.00, 0.67], 0.0259		0.15 [0.03, 0.77], 0.0231	
OR [95%-CI]; p-value	0.73 [0.05, 10.39], 0.8139		0.02 [0.00, 0.56], 0.0009		0.11 [0.01, 0.77], 0.0112	
RD [95%-CI]; p-value	-0.05 [-0.45, 0.36], 0.8218		-0.48 [-0.97, 0.01], 0.0552		-0.28 [-0.60, 0.03], 0.0782	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	6/102 (5.9)	3/57 (5.3)	4/92 (4.3)	4/56 (7.1)	10/194 (5.2)	7/113 (6.2)
RR [95%-CI]; p-value	1.12 [0.29, 4.30], 0.8715		0.61 [0.16, 2.34], 0.4696		0.83 [0.33, 2.13], 0.7008	
OR [95%-CI]; p-value	1.13 [0.27, 4.68], 0.8713		0.59 [0.14, 2.46], 0.4658		0.82 [0.30, 2.23], 0.7008	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8694		-0.03 [-0.11, 0.05], 0.4896		-0.01 [-0.06, 0.04], 0.7071	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_3_m_pt_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.8.1.1.s7.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6586		0.2684		0.2940	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	NA		0.07 [0.00, 1.84], 0.1116		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	NA		0.06 [0.00, 2.03], 0.0419		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	NA		-0.23 [-0.66, 0.20], 0.2876		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	2/102 (2.0)	1/57 (1.8)	2/92 (2.2)	2/56 (3.6)	4/194 (2.1)	3/113 (2.7)
RR [95%-CI]; p-value	1.12 [0.10, 12.06], 0.9270		0.61 [0.09, 4.20], 0.6145		0.78 [0.18, 3.41], 0.7376	
OR [95%-CI]; p-value	1.12 [0.10, 12.63], 0.9269		0.60 [0.08, 4.38], 0.6111		0.77 [0.17, 3.51], 0.7371	
RD [95%-CI]; p-value	0.00 [-0.04, 0.05], 0.9258		-0.01 [-0.07, 0.04], 0.6309		-0.01 [-0.04, 0.03], 0.7451	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_8_1_1_m_soc_sae5pct_dose_pp.sas using SAS 9.4

Table 12.4.8.1.2.s7.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_8_1_2_m_pt_sae5pct_dose_pp.sas using SAS 9.4

Table 12.4.5.1.1.s7.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_5_1_1_m_soc_aeg35pct_dose_pp.sas using SAS 9.4

Table 12.4.5.1.2.s7.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_5_1_2_m_pt_aeg35pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6898		0.4224		0.7715	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	6/27 (22.2)	1/4 (25.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.89 [0.14, 5.59], 0.9001		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.86 [0.07, 9.82], 0.9013		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.03 [-0.48, 0.42], 0.9042		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	20/102 (19.6)	17/57 (29.8)	17/92 (18.5)	5/56 (8.9)	37/194 (19.1)	22/113 (19.5)
RR [95%-CI]; p-value	0.66 [0.38, 1.15], 0.1417		2.07 [0.81, 5.30], 0.1294		0.98 [0.61, 1.57], 0.9321	
OR [95%-CI]; p-value	0.57 [0.27, 1.21], 0.1437		2.31 [0.80, 6.66], 0.1132		0.97 [0.54, 1.75], 0.9322	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.04], 0.1572		0.10 [-0.01, 0.20], 0.0858		-0.00 [-0.10, 0.09], 0.9323	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.2048		0.2380		0.0520	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	2/27 (7.4)	1/4 (25.0)	2/40 (5.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.30 [0.03, 2.57], 0.2694		0.15 [0.03, 0.77], 0.0231	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.24 [0.02, 3.51], 0.2667		0.11 [0.01, 0.77], 0.0112	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.18 [-0.61, 0.26], 0.4287		-0.28 [-0.60, 0.03], 0.0782	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	15/102 (14.7)	13/57 (22.8)	12/92 (13.0)	6/56 (10.7)	27/194 (13.9)	19/113 (16.8)
RR [95%-CI]; p-value	0.64 [0.33, 1.26], 0.1981		1.22 [0.48, 3.06], 0.6758		0.83 [0.48, 1.42], 0.4919	
OR [95%-CI]; p-value	0.58 [0.26, 1.33], 0.1984		1.25 [0.44, 3.54], 0.6742		0.80 [0.42, 1.52], 0.4928	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2177		0.02 [-0.08, 0.13], 0.6676		-0.03 [-0.11, 0.06], 0.5013	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.4561		0.7089		0.3445	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	5/27 (18.5)	1/4 (25.0)	8/40 (20.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		0.74 [0.11, 4.82], 0.7535		0.60 [0.20, 1.83], 0.3682	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		0.68 [0.06, 8.00], 0.7594		0.50 [0.10, 2.45], 0.3864	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		-0.06 [-0.51, 0.38], 0.7772		-0.13 [-0.47, 0.20], 0.4312	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	28/102 (27.5)	15/57 (26.3)	23/92 (25.0)	13/56 (23.2)	51/194 (26.3)	28/113 (24.8)
RR [95%-CI]; p-value	1.04 [0.61, 1.78], 0.8775		1.08 [0.59, 1.95], 0.8066		1.06 [0.71, 1.58], 0.7711	
OR [95%-CI]; p-value	1.06 [0.51, 2.20], 0.8772		1.10 [0.51, 2.40], 0.8060		1.08 [0.64, 1.85], 0.7704	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8767		0.02 [-0.12, 0.16], 0.8048		0.02 [-0.09, 0.12], 0.7692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.8726		0.5526		0.9650	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	3/40 (7.5)	0/9 (0.0)
RR [95%-CI]; p-value	0.85 [0.03, 21.72], 0.9196		0.67 [0.04, 12.53], 0.7865		1.43 [0.08, 26.14], 0.8114	
OR [95%-CI]; p-value	0.83 [0.02, 29.05], 0.9198		0.64 [0.02, 16.90], 0.7879		1.46 [0.07, 31.79], 0.8090	
RD [95%-CI]; p-value	-0.01 [-0.29, 0.27], 0.9222		-0.04 [-0.34, 0.27], 0.8129		0.02 [-0.14, 0.19], 0.7889	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	10/102 (9.8)	5/57 (8.8)	6/92 (6.5)	2/56 (3.6)	16/194 (8.2)	7/113 (6.2)
RR [95%-CI]; p-value	1.12 [0.40, 3.11], 0.8313		1.83 [0.38, 8.74], 0.4509		1.33 [0.56, 3.14], 0.5129	
OR [95%-CI]; p-value	1.13 [0.37, 3.49], 0.8309		1.88 [0.37, 9.67], 0.4414		1.36 [0.54, 3.42], 0.5100	
RD [95%-CI]; p-value	0.01 [-0.08, 0.10], 0.8286		0.03 [-0.04, 0.10], 0.4091		0.02 [-0.04, 0.08], 0.4949	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.7399		0.7681		0.9759	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	4/27 (14.8)	0/4 (0.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		1.33 [0.08, 21.18], 0.8384		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		1.39 [0.06, 31.69], 0.8353		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		0.04 [-0.28, 0.36], 0.8204		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	8/57 (14.0)	7/92 (7.6)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.77 [0.33, 1.80], 0.5440		0.85 [0.28, 2.56], 0.7753		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.74 [0.28, 1.96], 0.5445		0.84 [0.25, 2.79], 0.7754		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.5568		-0.01 [-0.11, 0.08], 0.7792		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0212		0.0518		0.0003	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	5/5 (100.0)	3/27 (11.1)	2/4 (50.0)	4/40 (10.0)	7/9 (77.8)
RR [95%-CI]; p-value	0.08 [0.01, 0.57], 0.0109		0.22 [0.05, 0.95], 0.0419		0.13 [0.05, 0.35], <0.0001	
OR [95%-CI]; p-value	0.01 [0.00, 0.29], 0.0005		0.13 [0.01, 1.24], 0.0484		0.03 [0.00, 0.21], <0.0001	
RD [95%-CI]; p-value	-0.83 [-1.00, -0.55], <0.0001		-0.39 [-0.89, 0.12], 0.1305		-0.68 [-0.96, -0.39], <0.0001	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	22/102 (21.6)	14/57 (24.6)	18/92 (19.6)	10/56 (17.9)	40/194 (20.6)	24/113 (21.2)
RR [95%-CI]; p-value	0.88 [0.49, 1.58], 0.6641		1.10 [0.55, 2.20], 0.7976		0.97 [0.62, 1.52], 0.8972	
OR [95%-CI]; p-value	0.84 [0.39, 1.82], 0.6654		1.12 [0.48, 2.63], 0.7969		0.96 [0.55, 1.70], 0.8973	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6693		0.02 [-0.11, 0.15], 0.7952		-0.01 [-0.10, 0.09], 0.8976	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.6775		0.8376		0.8733	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	3/27 (11.1)	0/4 (0.0)	5/40 (12.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		1.00 [0.06, 16.82], 1.0000		0.56 [0.13, 2.45], 0.4436	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		1.00 [0.04, 23.94], 1.0000		0.50 [0.08, 3.12], 0.4514	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		0.00 [-0.31, 0.31], 1.0000		-0.10 [-0.39, 0.19], 0.5116	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	18/102 (17.6)	18/57 (31.6)	17/92 (18.5)	14/56 (25.0)	35/194 (18.0)	32/113 (28.3)
RR [95%-CI]; p-value	0.56 [0.32, 0.99], 0.0444		0.74 [0.40, 1.38], 0.3428		0.64 [0.42, 0.97], 0.0352	
OR [95%-CI]; p-value	0.46 [0.22, 0.99], 0.0441		0.68 [0.30, 1.52], 0.3444		0.56 [0.32, 0.96], 0.0355	
RD [95%-CI]; p-value	-0.14 [-0.28, 0.00], 0.0537		-0.07 [-0.20, 0.07], 0.3557		-0.10 [-0.20, -0.00], 0.0422	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.4803		0.1299		0.0962	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	1/5 (20.0)	1/27 (3.7)	1/4 (25.0)	1/40 (2.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.19 [0.01, 4.71], 0.3071		0.15 [0.01, 1.93], 0.1446		0.11 [0.01, 1.11], 0.0614	
OR [95%-CI]; p-value	0.15 [0.00, 5.49], 0.2541		0.12 [0.01, 2.36], 0.1057		0.09 [0.01, 1.13], 0.0258	
RD [95%-CI]; p-value	-0.16 [-0.53, 0.20], 0.3813		-0.21 [-0.64, 0.22], 0.3320		-0.20 [-0.47, 0.08], 0.1612	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	10/57 (17.5)	12/92 (13.0)	6/56 (10.7)	23/194 (11.9)	16/113 (14.2)
RR [95%-CI]; p-value	0.61 [0.28, 1.36], 0.2289		1.22 [0.48, 3.06], 0.6758		0.84 [0.46, 1.52], 0.5582	
OR [95%-CI]; p-value	0.57 [0.23, 1.43], 0.2273		1.25 [0.44, 3.54], 0.6742		0.82 [0.41, 1.62], 0.5589	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.05], 0.2519		0.02 [-0.08, 0.13], 0.6676		-0.02 [-0.10, 0.06], 0.5664	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3645		0.4617		0.2116	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	4/27 (14.8)	1/4 (25.0)	6/40 (15.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		0.59 [0.09, 4.06], 0.5939		0.45 [0.14, 1.47], 0.1856	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		0.52 [0.04, 6.36], 0.6052		0.35 [0.07, 1.81], 0.1994	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		-0.10 [-0.55, 0.34], 0.6537		-0.18 [-0.51, 0.14], 0.2722	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	13/102 (12.7)	8/57 (14.0)	9/92 (9.8)	4/56 (7.1)	22/194 (11.3)	12/113 (10.6)
RR [95%-CI]; p-value	0.91 [0.40, 2.06], 0.8175		1.37 [0.44, 4.24], 0.5854		1.07 [0.55, 2.07], 0.8463	
OR [95%-CI]; p-value	0.89 [0.35, 2.31], 0.8178		1.41 [0.41, 4.81], 0.5822		1.08 [0.51, 2.27], 0.8461	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.10], 0.8198		0.03 [-0.06, 0.12], 0.5686		0.01 [-0.07, 0.08], 0.8450	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9887		0.0816		0.2511	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	NA		0.07 [0.00, 1.84], 0.1116		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	NA		0.06 [0.00, 2.03], 0.0419		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	NA		-0.23 [-0.66, 0.20], 0.2876		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	6/102 (5.9)	8/57 (14.0)	12/92 (13.0)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.42 [0.15, 1.15], 0.0908		1.46 [0.54, 3.93], 0.4525		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.38 [0.13, 1.17], 0.0819		1.53 [0.51, 4.60], 0.4464		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.08 [-0.18, 0.02], 0.1139		0.04 [-0.06, 0.14], 0.4271		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.6758		0.0604		0.1503	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	0/27 (0.0)	2/4 (50.0)	3/40 (7.5)	3/9 (33.3)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.04 [0.00, 0.67], 0.0259		0.23 [0.05, 0.94], 0.0406	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.02 [0.00, 0.56], 0.0009		0.16 [0.03, 1.00], 0.0327	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.48 [-0.97, 0.01], 0.0552		-0.26 [-0.58, 0.06], 0.1120	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	9/102 (8.8)	7/57 (12.3)	6/92 (6.5)	5/56 (8.9)	15/194 (7.7)	12/113 (10.6)
RR [95%-CI]; p-value	0.72 [0.28, 1.83], 0.4874		0.73 [0.23, 2.28], 0.5890		0.73 [0.35, 1.50], 0.3895	
OR [95%-CI]; p-value	0.69 [0.24, 1.97], 0.4871		0.71 [0.21, 2.45], 0.5882		0.71 [0.32, 1.57], 0.3889	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5041		-0.02 [-0.11, 0.07], 0.6007		-0.03 [-0.10, 0.04], 0.4060	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.4.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5249		0.1886		0.9615	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	2/40 (5.0)	1/9 (11.1)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.33 [0.01, 8.55], 0.5069		0.45 [0.05, 4.44], 0.4941	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.31 [0.01, 10.76], 0.4945		0.42 [0.03, 5.23], 0.4896	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.07 [-0.37, 0.22], 0.6273		-0.06 [-0.28, 0.16], 0.5795	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	3/102 (2.9)	11/57 (19.3)	5/92 (5.4)	0/56 (0.0)	8/194 (4.1)	11/113 (9.7)
RR [95%-CI]; p-value	0.15 [0.04, 0.52], 0.0028		6.14 [0.34, 110.30], 0.2181		0.42 [0.18, 1.02], 0.0559	
OR [95%-CI]; p-value	0.13 [0.03, 0.48], 0.0005		6.44 [0.34, 120.12], 0.1541		0.40 [0.16, 1.02], 0.0491	
RD [95%-CI]; p-value	-0.16 [-0.27, -0.06], 0.0029		0.05 [-0.01, 0.10], 0.0886		-0.06 [-0.12, 0.01], 0.0733	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_4_m_pt_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.3561		0.7328		0.7705	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	4/40 (10.0)	1/9 (11.1)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.33 [0.01, 8.55], 0.5069		0.90 [0.11, 7.12], 0.9205	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.31 [0.01, 10.76], 0.4945		0.89 [0.09, 9.06], 0.9207	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.07 [-0.37, 0.22], 0.6273		-0.01 [-0.24, 0.21], 0.9230	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	8/102 (7.8)	1/57 (1.8)	5/92 (5.4)	5/56 (8.9)	13/194 (6.7)	6/113 (5.3)
RR [95%-CI]; p-value	4.47 [0.57, 34.85], 0.1529		0.61 [0.18, 2.01], 0.4152		1.26 [0.49, 3.23], 0.6272	
OR [95%-CI]; p-value	4.77 [0.58, 39.12], 0.1111		0.59 [0.16, 2.12], 0.4115		1.28 [0.47, 3.47], 0.6256	
RD [95%-CI]; p-value	0.06 [-0.00, 0.12], 0.0555		-0.03 [-0.12, 0.05], 0.4359		0.01 [-0.04, 0.07], 0.6155	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.6945		NA		0.5394	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	1/102 (1.0)	0/57 (0.0)	0/92 (0.0)	0/56 (0.0)	1/194 (0.5)	0/113 (0.0)
RR [95%-CI]; p-value	1.13 [0.04, 33.09], 0.9445		NA		1.17 [0.04, 34.60], 0.9276	
OR [95%-CI]; p-value	1.13 [0.04, 34.17], 0.9445		NA		1.17 [0.04, 35.18], 0.9275	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9436		NA		0.00 [-0.02, 0.02], 0.9260	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4074		0.7328		0.8242	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	4/40 (10.0)	1/9 (11.1)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.33 [0.01, 8.55], 0.5069		0.90 [0.11, 7.12], 0.9205	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.31 [0.01, 10.76], 0.4945		0.89 [0.09, 9.06], 0.9207	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.07 [-0.37, 0.22], 0.6273		-0.01 [-0.24, 0.21], 0.9230	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	7/102 (6.9)	1/57 (1.8)	5/92 (5.4)	5/56 (8.9)	12/194 (6.2)	6/113 (5.3)
RR [95%-CI]; p-value	3.91 [0.49, 31.00], 0.1966		0.61 [0.18, 2.01], 0.4152		1.16 [0.45, 3.02], 0.7533	
OR [95%-CI]; p-value	4.13 [0.49, 34.42], 0.1576		0.59 [0.16, 2.12], 0.4115		1.18 [0.43, 3.22], 0.7527	
RD [95%-CI]; p-value	0.05 [-0.01, 0.11], 0.0937		-0.03 [-0.12, 0.05], 0.4359		0.01 [-0.04, 0.06], 0.7481	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.2152		0.4366		0.1054	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	0/27 (0.0)	0/4 (0.0)	1/40 (2.5)	1/9 (11.1)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		NA		0.23 [0.02, 3.27], 0.2746	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		NA		0.21 [0.01, 3.63], 0.2381	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		NA		-0.09 [-0.30, 0.12], 0.4237	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	4/102 (3.9)	0/57 (0.0)	1/92 (1.1)	0/56 (0.0)	5/194 (2.6)	0/113 (0.0)
RR [95%-CI]; p-value	4.51 [0.24, 83.80], 0.3124		1.23 [0.04, 36.02], 0.9051		5.85 [0.32, 106.10], 0.2322	
OR [95%-CI]; p-value	4.65 [0.24, 89.62], 0.2637		1.23 [0.04, 37.29], 0.9049		5.98 [0.32, 110.46], 0.1725	
RD [95%-CI]; p-value	0.03 [-0.01, 0.08], 0.1805		0.00 [-0.03, 0.03], 0.9025		0.02 [-0.00, 0.05], 0.0993	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8316		0.8779		0.8516	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	2/40 (5.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		0.67 [0.04, 12.53], 0.7865		0.95 [0.05, 19.41], 0.9734	
OR [95%-CI]; p-value	NA		0.64 [0.02, 16.90], 0.7879		0.95 [0.04, 22.85], 0.9734	
RD [95%-CI]; p-value	NA		-0.04 [-0.34, 0.27], 0.8129		-0.00 [-0.16, 0.15], 0.9738	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	10/102 (9.8)	9/57 (15.8)	7/92 (7.6)	5/56 (8.9)	17/194 (8.8)	14/113 (12.4)
RR [95%-CI]; p-value	0.62 [0.27, 1.44], 0.2663		0.85 [0.28, 2.56], 0.7753		0.71 [0.36, 1.38], 0.3098	
OR [95%-CI]; p-value	0.58 [0.22, 1.52], 0.2645		0.84 [0.25, 2.79], 0.7754		0.68 [0.32, 1.44], 0.3091	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.2900		-0.01 [-0.11, 0.08], 0.7792		-0.04 [-0.11, 0.04], 0.3277	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.6945		0.3794		0.3780	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	1/102 (1.0)	0/57 (0.0)	2/92 (2.2)	1/56 (1.8)	3/194 (1.5)	1/113 (0.9)
RR [95%-CI]; p-value	1.13 [0.04, 33.09], 0.9445		1.22 [0.11, 13.12], 0.8712		1.75 [0.18, 16.60], 0.6270	
OR [95%-CI]; p-value	1.13 [0.04, 34.17], 0.9445		1.22 [0.11, 13.80], 0.8709		1.76 [0.18, 17.12], 0.6221	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9436		0.00 [-0.04, 0.05], 0.8679		0.01 [-0.02, 0.03], 0.5965	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.8735		0.9546		0.7902	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	2/40 (5.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		0.67 [0.04, 12.53], 0.7865		0.95 [0.05, 19.41], 0.9734	
OR [95%-CI]; p-value	NA		0.64 [0.02, 16.90], 0.7879		0.95 [0.04, 22.85], 0.9734	
RD [95%-CI]; p-value	NA		-0.04 [-0.34, 0.27], 0.8129		-0.00 [-0.16, 0.15], 0.9738	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	9/102 (8.8)	9/57 (15.8)	6/92 (6.5)	5/56 (8.9)	15/194 (7.7)	14/113 (12.4)
RR [95%-CI]; p-value	0.56 [0.24, 1.33], 0.1874		0.73 [0.23, 2.28], 0.5890		0.62 [0.31, 1.24], 0.1808	
OR [95%-CI]; p-value	0.52 [0.19, 1.39], 0.1837		0.71 [0.21, 2.45], 0.5882		0.59 [0.27, 1.28], 0.1784	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2125		-0.02 [-0.11, 0.07], 0.6007		-0.05 [-0.12, 0.02], 0.2013	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.3250		0.2829		0.2016	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	4/102 (3.9)	0/57 (0.0)	3/92 (3.3)	1/56 (1.8)	7/194 (3.6)	1/113 (0.9)
RR [95%-CI]; p-value	4.51 [0.24, 83.80], 0.3124		1.83 [0.19, 17.13], 0.5980		4.08 [0.51, 32.72], 0.1859	
OR [95%-CI]; p-value	4.65 [0.24, 89.62], 0.2637		1.85 [0.19, 18.27], 0.5915		4.19 [0.51, 34.52], 0.1486	
RD [95%-CI]; p-value	0.03 [-0.01, 0.08], 0.1805		0.01 [-0.04, 0.06], 0.5647		0.03 [-0.00, 0.06], 0.0893	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.6.s7.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.8190		0.2721		0.5519	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	4/27 (14.8)	1/4 (25.0)	5/40 (12.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.59 [0.09, 4.06], 0.5939		0.56 [0.13, 2.45], 0.4436	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.52 [0.04, 6.36], 0.6052		0.50 [0.08, 3.12], 0.4514	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.10 [-0.55, 0.34], 0.6537		-0.10 [-0.39, 0.19], 0.5116	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	15/102 (14.7)	16/57 (28.1)	19/92 (20.7)	6/56 (10.7)	34/194 (17.5)	22/113 (19.5)
RR [95%-CI]; p-value	0.52 [0.28, 0.98], 0.0428		1.93 [0.82, 4.54], 0.1328		0.90 [0.56, 1.46], 0.6699	
OR [95%-CI]; p-value	0.44 [0.20, 0.98], 0.0414		2.17 [0.81, 5.81], 0.1176		0.88 [0.48, 1.59], 0.6707	
RD [95%-CI]; p-value	-0.13 [-0.27, 0.00], 0.0530		0.10 [-0.02, 0.22], 0.0925		-0.02 [-0.11, 0.07], 0.6739	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_6_m_pt_adr_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.1629		0.5568		0.0925	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	10/15 (66.7)	10/10 (100.0)	12/19 (63.2)	6/8 (75.0)	22/34 (64.7)	16/18 (88.9)
RR [95%-CI]; p-value	0.70 [0.48, 1.03], 0.0676		0.84 [0.50, 1.43], 0.5229		0.73 [0.54, 0.98], 0.0362	
OR [95%-CI]; p-value	0.10 [0.00, 2.08], 0.0843		0.57 [0.09, 3.64], 0.5511		0.23 [0.04, 1.17], 0.0614	
RD [95%-CI]; p-value	-0.29 [-0.56, -0.01], 0.0389		-0.12 [-0.49, 0.25], 0.5307		-0.24 [-0.46, -0.03], 0.0286	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	73/100 (73.0)	40/52 (76.9)	60/100 (60.0)	31/52 (59.6)	133/200 (66.5)	71/104 (68.3)
RR [95%-CI]; p-value	0.95 [0.78, 1.15], 0.5906		1.01 [0.76, 1.33], 0.9634		0.97 [0.83, 1.15], 0.7534	
OR [95%-CI]; p-value	0.81 [0.37, 1.77], 0.5993		1.02 [0.51, 2.01], 0.9634		0.92 [0.56, 1.53], 0.7554	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.10], 0.5929		0.00 [-0.16, 0.17], 0.9634		-0.02 [-0.13, 0.09], 0.7543	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.1089		0.3430		0.0658	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	4/10 (40.0)	3/19 (15.8)	1/8 (12.5)	4/34 (11.8)	5/18 (27.8)
RR [95%-CI]; p-value	0.17 [0.02, 1.28], 0.0852		1.26 [0.15, 10.39], 0.8280		0.42 [0.13, 1.38], 0.1550	
OR [95%-CI]; p-value	0.11 [0.01, 1.17], 0.0412		1.31 [0.12, 14.93], 0.8261		0.35 [0.08, 1.50], 0.1465	
RD [95%-CI]; p-value	-0.33 [-0.66, -0.00], 0.0469		0.03 [-0.25, 0.31], 0.8190		-0.16 [-0.39, 0.07], 0.1790	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	12/100 (12.0)	6/52 (11.5)	10/100 (10.0)	1/52 (1.9)	22/200 (11.0)	7/104 (6.7)
RR [95%-CI]; p-value	1.04 [0.41, 2.61], 0.9335		5.20 [0.68, 39.52], 0.1111		1.63 [0.72, 3.70], 0.2386	
OR [95%-CI]; p-value	1.05 [0.37, 2.97], 0.9334		5.67 [0.71, 45.55], 0.0683		1.71 [0.71, 4.15], 0.2293	
RD [95%-CI]; p-value	0.00 [-0.10, 0.11], 0.9331		0.08 [0.01, 0.15], 0.0230		0.04 [-0.02, 0.11], 0.1966	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.6380		0.3455		0.5701	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	2/18 (11.1)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.10 [0.01, 2.03], 0.1352		0.53 [0.08, 3.45], 0.5061	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.08 [0.00, 2.00], 0.0631		0.50 [0.06, 3.88], 0.5008	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.22 [-0.53, 0.08], 0.1536		-0.05 [-0.22, 0.11], 0.5353	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	4/52 (7.7)	3/100 (3.0)	3/52 (5.8)	13/200 (6.5)	7/104 (6.7)
RR [95%-CI]; p-value	1.30 [0.43, 3.94], 0.6432		0.52 [0.11, 2.49], 0.4128		0.97 [0.40, 2.35], 0.9386	
OR [95%-CI]; p-value	1.33 [0.40, 4.48], 0.6407		0.51 [0.10, 2.60], 0.4055		0.96 [0.37, 2.49], 0.9386	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6278		-0.03 [-0.10, 0.04], 0.4488		-0.00 [-0.06, 0.06], 0.9389	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.2153		0.1787		0.8975	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	5/15 (33.3)	1/10 (10.0)	1/19 (5.3)	2/8 (25.0)	6/34 (17.6)	3/18 (16.7)
RR [95%-CI]; p-value	3.33 [0.45, 24.44], 0.2363		0.21 [0.02, 2.01], 0.1754		1.06 [0.30, 3.74], 0.9293	
OR [95%-CI]; p-value	4.50 [0.44, 46.17], 0.1808		0.17 [0.01, 2.18], 0.1362		1.07 [0.23, 4.90], 0.9292	
RD [95%-CI]; p-value	0.23 [-0.07, 0.54], 0.1305		-0.20 [-0.51, 0.12], 0.2215		0.01 [-0.20, 0.22], 0.9287	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	15/100 (15.0)	9/52 (17.3)	11/100 (11.0)	5/52 (9.6)	26/200 (13.0)	14/104 (13.5)
RR [95%-CI]; p-value	0.87 [0.41, 1.84], 0.7104		1.14 [0.42, 3.12], 0.7926		0.97 [0.53, 1.77], 0.9100	
OR [95%-CI]; p-value	0.84 [0.34, 2.08], 0.7113		1.16 [0.38, 3.54], 0.7919		0.96 [0.48, 1.93], 0.9101	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.10], 0.7161		0.01 [-0.09, 0.11], 0.7880		-0.00 [-0.09, 0.08], 0.9105	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.7406		0.4914		0.3833	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	4/15 (26.7)	2/10 (20.0)	1/19 (5.3)	0/8 (0.0)	5/34 (14.7)	2/18 (11.1)
RR [95%-CI]; p-value	1.33 [0.30, 5.96], 0.7064		0.89 [0.03, 24.19], 0.9473		1.32 [0.28, 6.16], 0.7208	
OR [95%-CI]; p-value	1.45 [0.21, 9.98], 0.7022		0.89 [0.03, 29.30], 0.9473		1.38 [0.24, 7.94], 0.7179	
RD [95%-CI]; p-value	0.07 [-0.27, 0.40], 0.6956		-0.01 [-0.19, 0.18], 0.9484		0.04 [-0.15, 0.22], 0.7075	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	1/52 (1.9)	4/100 (4.0)	0/52 (0.0)	8/200 (4.0)	1/104 (1.0)
RR [95%-CI]; p-value	2.08 [0.24, 18.14], 0.5074		4.20 [0.23, 77.94], 0.3356		4.16 [0.53, 32.81], 0.1761	
OR [95%-CI]; p-value	2.13 [0.23, 19.52], 0.4958		4.33 [0.22, 83.56], 0.2907		4.29 [0.53, 34.79], 0.1381	
RD [95%-CI]; p-value	0.02 [-0.03, 0.07], 0.4472		0.03 [-0.02, 0.08], 0.1993		0.03 [-0.00, 0.06], 0.0712	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9126		NA		0.9899	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	1/52 (1.9)	0/100 (0.0)	0/52 (0.0)	1/200 (0.5)	1/104 (1.0)
RR [95%-CI]; p-value	0.52 [0.03, 8.15], 0.6413		NA		0.52 [0.03, 8.23], 0.6426	
OR [95%-CI]; p-value	0.52 [0.03, 8.41], 0.6356		NA		0.52 [0.03, 8.36], 0.6368	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.6675		NA		-0.00 [-0.03, 0.02], 0.6689	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7122		NA		0.7822	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	0/100 (0.0)	1/52 (1.9)	0/100 (0.0)	0/52 (0.0)	0/200 (0.0)	1/104 (1.0)
RR [95%-CI]; p-value	0.26 [0.01, 7.58], 0.4328		NA		0.26 [0.01, 7.67], 0.4348	
OR [95%-CI]; p-value	0.26 [0.01, 7.73], 0.3978		NA		0.26 [0.01, 7.74], 0.3999	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.4825		NA		-0.01 [-0.03, 0.01], 0.4849	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.0482		0.9385		0.1440	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	6/15 (40.0)	9/10 (90.0)	12/19 (63.2)	5/8 (62.5)	18/34 (52.9)	14/18 (77.8)
RR [95%-CI]; p-value	0.44 [0.23, 0.85], 0.0150		1.01 [0.53, 1.91], 0.9743		0.68 [0.46, 1.02], 0.0606	
OR [95%-CI]; p-value	0.07 [0.01, 0.75], 0.0124		1.03 [0.19, 5.68], 0.9742		0.32 [0.09, 1.18], 0.0799	
RD [95%-CI]; p-value	-0.50 [-0.81, -0.19], 0.0016		0.01 [-0.39, 0.41], 0.9743		-0.25 [-0.50, 0.01], 0.0563	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	62/100 (62.0)	36/52 (69.2)	48/100 (48.0)	24/52 (46.2)	110/200 (55.0)	60/104 (57.7)
RR [95%-CI]; p-value	0.90 [0.71, 1.14], 0.3625		1.04 [0.73, 1.49], 0.8297		0.95 [0.78, 1.17], 0.6507	
OR [95%-CI]; p-value	0.73 [0.36, 1.48], 0.3769		1.08 [0.55, 2.11], 0.8288		0.90 [0.56, 1.45], 0.6538	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.09], 0.3680		0.02 [-0.15, 0.19], 0.8286		-0.03 [-0.14, 0.09], 0.6529	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.4263		0.1177		0.5989	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	7/15 (46.7)	4/10 (40.0)	5/19 (26.3)	4/8 (50.0)	12/34 (35.3)	8/18 (44.4)
RR [95%-CI]; p-value	1.17 [0.46, 2.96], 0.7458		0.53 [0.19, 1.46], 0.2187		0.79 [0.40, 1.58], 0.5116	
OR [95%-CI]; p-value	1.31 [0.26, 6.64], 0.7422		0.36 [0.06, 2.00], 0.2332		0.68 [0.21, 2.19], 0.5188	
RD [95%-CI]; p-value	0.07 [-0.33, 0.46], 0.7407		-0.24 [-0.64, 0.16], 0.2447		-0.09 [-0.37, 0.19], 0.5221	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	31/100 (31.0)	21/52 (40.4)	31/100 (31.0)	12/52 (23.1)	62/200 (31.0)	33/104 (31.7)
RR [95%-CI]; p-value	0.77 [0.49, 1.19], 0.2399		1.34 [0.76, 2.39], 0.3152		0.98 [0.69, 1.39], 0.8961	
OR [95%-CI]; p-value	0.66 [0.33, 1.33], 0.2473		1.50 [0.69, 3.24], 0.3035		0.97 [0.58, 1.61], 0.8962	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.07], 0.2540		0.08 [-0.07, 0.23], 0.2877		-0.01 [-0.12, 0.10], 0.8964	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.6380		0.3455		0.5701	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	2/18 (11.1)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.10 [0.01, 2.03], 0.1352		0.53 [0.08, 3.45], 0.5061	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.08 [0.00, 2.00], 0.0631		0.50 [0.06, 3.88], 0.5008	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.22 [-0.53, 0.08], 0.1536		-0.05 [-0.22, 0.11], 0.5353	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	4/52 (7.7)	3/100 (3.0)	3/52 (5.8)	13/200 (6.5)	7/104 (6.7)
RR [95%-CI]; p-value	1.30 [0.43, 3.94], 0.6432		0.52 [0.11, 2.49], 0.4128		0.97 [0.40, 2.35], 0.9386	
OR [95%-CI]; p-value	1.33 [0.40, 4.48], 0.6407		0.51 [0.10, 2.60], 0.4055		0.96 [0.37, 2.49], 0.9386	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6278		-0.03 [-0.10, 0.04], 0.4488		-0.00 [-0.06, 0.06], 0.9389	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.8734		0.7653		0.6599	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	3/10 (30.0)	1/19 (5.3)	0/8 (0.0)	3/34 (8.8)	3/18 (16.7)
RR [95%-CI]; p-value	0.44 [0.09, 2.20], 0.3206		0.89 [0.03, 24.19], 0.9473		0.53 [0.12, 2.36], 0.4044	
OR [95%-CI]; p-value	0.36 [0.05, 2.68], 0.3074		0.89 [0.03, 29.30], 0.9473		0.48 [0.09, 2.69], 0.3997	
RD [95%-CI]; p-value	-0.17 [-0.50, 0.17], 0.3252		-0.01 [-0.19, 0.18], 0.9484		-0.08 [-0.28, 0.12], 0.4347	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	6/100 (6.0)	2/52 (3.8)	12/200 (6.0)	8/104 (7.7)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		1.56 [0.33, 7.46], 0.5775		0.78 [0.33, 1.85], 0.5724	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		1.60 [0.31, 8.20], 0.5726		0.77 [0.30, 1.94], 0.5723	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.02 [-0.05, 0.09], 0.5464		-0.02 [-0.08, 0.04], 0.5859	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6511		0.5234		0.7846	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	3/10 (30.0)	6/19 (31.6)	2/8 (25.0)	8/34 (23.5)	5/18 (27.8)
RR [95%-CI]; p-value	0.44 [0.09, 2.20], 0.3206		1.26 [0.32, 4.97], 0.7383		0.85 [0.32, 2.21], 0.7348	
OR [95%-CI]; p-value	0.36 [0.05, 2.68], 0.3074		1.38 [0.21, 8.98], 0.7325		0.80 [0.22, 2.94], 0.7364	
RD [95%-CI]; p-value	-0.17 [-0.50, 0.17], 0.3252		0.07 [-0.30, 0.43], 0.7244		-0.04 [-0.29, 0.21], 0.7404	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	19/100 (19.0)	15/52 (28.8)	17/100 (17.0)	4/52 (7.7)	36/200 (18.0)	19/104 (18.3)
RR [95%-CI]; p-value	0.66 [0.37, 1.19], 0.1641		2.21 [0.78, 6.23], 0.1337		0.99 [0.60, 1.63], 0.9538	
OR [95%-CI]; p-value	0.58 [0.27, 1.26], 0.1670		2.46 [0.78, 7.73], 0.1146		0.98 [0.53, 1.82], 0.9539	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.05], 0.1837		0.09 [-0.01, 0.20], 0.0773		-0.00 [-0.09, 0.09], 0.9540	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.3993		0.0977		0.4155	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	1/10 (10.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	1.33 [0.14, 12.82], 0.8033		0.10 [0.01, 2.03], 0.1352		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	1.38 [0.11, 17.67], 0.8016		0.08 [0.00, 2.00], 0.0631		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	0.03 [-0.22, 0.29], 0.7965		-0.22 [-0.53, 0.08], 0.1536		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	13/100 (13.0)	14/52 (26.9)	14/100 (14.0)	5/52 (9.6)	27/200 (13.5)	19/104 (18.3)
RR [95%-CI]; p-value	0.48 [0.25, 0.95], 0.0349		1.46 [0.55, 3.82], 0.4452		0.74 [0.43, 1.26], 0.2695	
OR [95%-CI]; p-value	0.41 [0.17, 0.94], 0.0331		1.53 [0.52, 4.51], 0.4381		0.70 [0.37, 1.33], 0.2710	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0470		0.04 [-0.06, 0.15], 0.4135		-0.05 [-0.14, 0.04], 0.2886	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.8339		0.6020		0.7063	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	5/15 (33.3)	3/10 (30.0)	4/19 (21.1)	1/8 (12.5)	9/34 (26.5)	4/18 (22.2)
RR [95%-CI]; p-value	1.11 [0.34, 3.64], 0.8619		1.68 [0.22, 12.82], 0.6147		1.19 [0.43, 3.34], 0.7392	
OR [95%-CI]; p-value	1.17 [0.21, 6.56], 0.8611		1.87 [0.17, 19.93], 0.6014		1.26 [0.33, 4.85], 0.7364	
RD [95%-CI]; p-value	0.03 [-0.34, 0.40], 0.8602		0.09 [-0.21, 0.38], 0.5679		0.04 [-0.20, 0.29], 0.7315	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	26/100 (26.0)	14/52 (26.9)	24/100 (24.0)	13/52 (25.0)	50/200 (25.0)	27/104 (26.0)
RR [95%-CI]; p-value	0.97 [0.55, 1.68], 0.9022		0.96 [0.53, 1.72], 0.8914		0.96 [0.64, 1.44], 0.8546	
OR [95%-CI]; p-value	0.95 [0.45, 2.04], 0.9024		0.95 [0.44, 2.06], 0.8916		0.95 [0.55, 1.64], 0.8549	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9028		-0.01 [-0.15, 0.13], 0.8921		-0.01 [-0.11, 0.09], 0.8554	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.1739		0.0566		0.8560	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	4/15 (26.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	6/34 (17.6)	4/18 (22.2)
RR [95%-CI]; p-value	2.67 [0.35, 20.51], 0.3460		0.28 [0.06, 1.37], 0.1167		0.79 [0.26, 2.46], 0.6890	
OR [95%-CI]; p-value	3.27 [0.31, 34.72], 0.3074		0.20 [0.03, 1.52], 0.0994		0.75 [0.18, 3.10], 0.6904	
RD [95%-CI]; p-value	0.17 [-0.12, 0.46], 0.2616		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.28, 0.19], 0.6977	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	9/52 (17.3)	9/100 (9.0)	2/52 (3.8)	19/200 (9.5)	11/104 (10.6)
RR [95%-CI]; p-value	0.58 [0.25, 1.33], 0.1983		2.34 [0.52, 10.44], 0.2651		0.90 [0.44, 1.82], 0.7649	
OR [95%-CI]; p-value	0.53 [0.20, 1.40], 0.1962		2.47 [0.51, 11.89], 0.2446		0.89 [0.41, 1.94], 0.7652	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2266		0.05 [-0.03, 0.13], 0.1877		-0.01 [-0.08, 0.06], 0.7686	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5539		0.7262		0.9448	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	2/10 (20.0)	3/19 (15.8)	1/8 (12.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	0.33 [0.03, 3.20], 0.3414		1.26 [0.15, 10.39], 0.8280		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	0.29 [0.02, 3.67], 0.3149		1.31 [0.12, 14.93], 0.8261		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	-0.13 [-0.41, 0.14], 0.3476		0.03 [-0.25, 0.31], 0.8190		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	22/100 (22.0)	17/52 (32.7)	18/100 (18.0)	11/52 (21.2)	40/200 (20.0)	28/104 (26.9)
RR [95%-CI]; p-value	0.67 [0.39, 1.15], 0.1482		0.85 [0.43, 1.66], 0.6373		0.74 [0.49, 1.13], 0.1662	
OR [95%-CI]; p-value	0.58 [0.27, 1.23], 0.1522		0.82 [0.35, 1.89], 0.6387		0.68 [0.39, 1.18], 0.1694	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1656		-0.03 [-0.17, 0.10], 0.6449		-0.07 [-0.17, 0.03], 0.1821	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2827		0.1594		0.0868	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	5/10 (50.0)	3/19 (15.8)	4/8 (50.0)	5/34 (14.7)	9/18 (50.0)
RR [95%-CI]; p-value	0.27 [0.06, 1.12], 0.0703		0.32 [0.09, 1.10], 0.0703		0.29 [0.12, 0.75], 0.0101	
OR [95%-CI]; p-value	0.15 [0.02, 1.07], 0.0455		0.19 [0.03, 1.20], 0.0640		0.17 [0.05, 0.65], 0.0063	
RD [95%-CI]; p-value	-0.37 [-0.72, -0.01], 0.0426		-0.34 [-0.73, 0.04], 0.0802		-0.35 [-0.61, -0.09], 0.0078	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	18/100 (18.0)	15/52 (28.8)	17/100 (17.0)	10/52 (19.2)	35/200 (17.5)	25/104 (24.0)
RR [95%-CI]; p-value	0.62 [0.34, 1.13], 0.1220		0.88 [0.44, 1.79], 0.7320		0.73 [0.46, 1.15], 0.1717	
OR [95%-CI]; p-value	0.54 [0.25, 1.19], 0.1239		0.86 [0.36, 2.04], 0.7328		0.67 [0.38, 1.20], 0.1742	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.04], 0.1408		-0.02 [-0.15, 0.11], 0.7366		-0.07 [-0.16, 0.03], 0.1890	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8607		0.0979		0.3845	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.05, 9.47], 0.7646		0.28 [0.06, 1.37], 0.1167		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.64 [0.04, 11.63], 0.7634		0.20 [0.03, 1.52], 0.0994		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.19], 0.7713		-0.27 [-0.63, 0.09], 0.1450		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	10/52 (19.2)	11/100 (11.0)	4/52 (7.7)	21/200 (10.5)	14/104 (13.5)
RR [95%-CI]; p-value	0.52 [0.23, 1.17], 0.1136		1.43 [0.48, 4.27], 0.5217		0.78 [0.41, 1.47], 0.4420	
OR [95%-CI]; p-value	0.47 [0.18, 1.21], 0.1102		1.48 [0.45, 4.91], 0.5165		0.75 [0.37, 1.55], 0.4428	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1387		0.03 [-0.06, 0.13], 0.4945		-0.03 [-0.11, 0.05], 0.4577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3106		0.9364		0.3018	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	0/10 (0.0)	1/19 (5.3)	0/8 (0.0)	2/34 (5.9)	0/18 (0.0)
RR [95%-CI]; p-value	1.40 [0.05, 38.03], 0.8417		0.89 [0.03, 24.19], 0.9473		2.18 [0.10, 45.81], 0.6169	
OR [95%-CI]; p-value	1.43 [0.04, 46.86], 0.8406		0.89 [0.03, 29.30], 0.9473		2.25 [0.10, 52.63], 0.6053	
RD [95%-CI]; p-value	0.02 [-0.16, 0.20], 0.8360		-0.01 [-0.19, 0.18], 0.9484		0.03 [-0.08, 0.14], 0.5648	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	3/100 (3.0)	7/52 (13.5)	4/100 (4.0)	2/52 (3.8)	7/200 (3.5)	9/104 (8.7)
RR [95%-CI]; p-value	0.22 [0.06, 0.83], 0.0247		1.04 [0.20, 5.49], 0.9632		0.40 [0.16, 1.06], 0.0643	
OR [95%-CI]; p-value	0.20 [0.05, 0.80], 0.0136		1.04 [0.18, 5.88], 0.9631		0.38 [0.14, 1.06], 0.0562	
RD [95%-CI]; p-value	-0.10 [-0.20, -0.01], 0.0376		0.00 [-0.06, 0.07], 0.9629		-0.05 [-0.11, 0.01], 0.0908	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1844		0.5350		0.2212	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	3/10 (30.0)	4/19 (21.1)	2/8 (25.0)	5/34 (14.7)	5/18 (27.8)
RR [95%-CI]; p-value	0.22 [0.03, 1.85], 0.1638		0.84 [0.19, 3.71], 0.8203		0.53 [0.18, 1.59], 0.2572	
OR [95%-CI]; p-value	0.17 [0.01, 1.91], 0.1190		0.80 [0.11, 5.59], 0.8218		0.45 [0.11, 1.82], 0.2552	
RD [95%-CI]; p-value	-0.23 [-0.54, 0.08], 0.1412		-0.04 [-0.39, 0.31], 0.8258		-0.13 [-0.37, 0.11], 0.2832	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	14/100 (14.0)	7/52 (13.5)	9/100 (9.0)	3/52 (5.8)	23/200 (11.5)	10/104 (9.6)
RR [95%-CI]; p-value	1.04 [0.45, 2.42], 0.9274		1.56 [0.44, 5.52], 0.4901		1.20 [0.59, 2.42], 0.6181	
OR [95%-CI]; p-value	1.05 [0.39, 2.78], 0.9273		1.62 [0.42, 6.24], 0.4834		1.22 [0.56, 2.67], 0.6163	
RD [95%-CI]; p-value	0.01 [-0.11, 0.12], 0.9269		0.03 [-0.05, 0.12], 0.4543		0.02 [-0.05, 0.09], 0.6073	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4712		0.0323		0.0469	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	2/10 (20.0)	0/19 (0.0)	3/8 (37.5)	0/34 (0.0)	5/18 (27.8)
RR [95%-CI]; p-value	0.16 [0.01, 3.22], 0.2325		0.07 [0.00, 1.22], 0.0678		0.05 [0.00, 0.90], 0.0423	
OR [95%-CI]; p-value	0.13 [0.01, 3.32], 0.1643		0.04 [0.00, 1.03], 0.0125		0.04 [0.00, 0.75], 0.0031	
RD [95%-CI]; p-value	-0.17 [-0.43, 0.10], 0.2114		-0.35 [-0.69, -0.01], 0.0457		-0.26 [-0.47, -0.05], 0.0143	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	12/100 (12.0)	3/52 (5.8)	18/200 (9.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		2.08 [0.61, 7.05], 0.2394		1.04 [0.48, 2.23], 0.9199	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		2.23 [0.60, 8.28], 0.2217		1.04 [0.45, 2.41], 0.9198	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.06 [-0.03, 0.15], 0.1741		0.00 [-0.06, 0.07], 0.9194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.5594		0.9844		0.4465	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	1/10 (10.0)	1/19 (5.3)	1/8 (12.5)	1/34 (2.9)	2/18 (11.1)
RR [95%-CI]; p-value	0.32 [0.01, 8.75], 0.5016		0.42 [0.03, 5.93], 0.5217		0.26 [0.03, 2.72], 0.2638	
OR [95%-CI]; p-value	0.30 [0.01, 9.87], 0.4778		0.39 [0.02, 7.11], 0.5121		0.24 [0.02, 2.88], 0.2293	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.14], 0.5186		-0.07 [-0.32, 0.18], 0.5708		-0.08 [-0.24, 0.07], 0.3043	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	12/100 (12.0)	7/52 (13.5)	5/100 (5.0)	6/52 (11.5)	17/200 (8.5)	13/104 (12.5)
RR [95%-CI]; p-value	0.89 [0.37, 2.13], 0.7957		0.43 [0.14, 1.35], 0.1500		0.68 [0.34, 1.35], 0.2678	
OR [95%-CI]; p-value	0.88 [0.32, 2.38], 0.7960		0.40 [0.12, 1.39], 0.1399		0.65 [0.30, 1.40], 0.2673	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.10], 0.7991		-0.07 [-0.16, 0.03], 0.1854		-0.04 [-0.11, 0.03], 0.2919	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.6285		0.6892		0.7842	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	3/10 (30.0)	2/19 (10.5)	0/8 (0.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	0.11 [0.01, 1.93], 0.1300		1.79 [0.09, 35.64], 0.7030		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	0.08 [0.00, 1.77], 0.0551		1.88 [0.08, 46.68], 0.6954		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	-0.27 [-0.57, 0.03], 0.0776		0.05 [-0.16, 0.26], 0.6646		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	9/52 (17.3)	4/100 (4.0)	0/52 (0.0)	8/200 (4.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.23 [0.07, 0.71], 0.0110		4.20 [0.23, 77.94], 0.3356		0.46 [0.18, 1.16], 0.1011	
OR [95%-CI]; p-value	0.20 [0.06, 0.68], 0.0054		4.33 [0.22, 83.56], 0.2907		0.44 [0.16, 1.18], 0.0939	
RD [95%-CI]; p-value	-0.13 [-0.24, -0.02], 0.0175		0.03 [-0.02, 0.08], 0.1993		-0.05 [-0.11, 0.01], 0.1315	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_3_m_pt_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.6398		0.4752		0.5767	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	2/19 (10.5)	1/8 (12.5)	2/34 (5.9)	1/18 (5.6)
RR [95%-CI]; p-value	0.68 [0.01, 31.54], 0.8425		0.84 [0.09, 8.02], 0.8812		1.06 [0.10, 10.90], 0.9617	
OR [95%-CI]; p-value	0.67 [0.01, 36.43], 0.8416		0.82 [0.06, 10.62], 0.8815		1.06 [0.09, 12.58], 0.9616	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8469		-0.02 [-0.29, 0.25], 0.8850		0.00 [-0.13, 0.14], 0.9613	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	8/52 (15.4)	5/100 (5.0)	1/52 (1.9)	9/200 (4.5)	9/104 (8.7)
RR [95%-CI]; p-value	0.26 [0.08, 0.82], 0.0220		2.60 [0.31, 21.68], 0.3772		0.52 [0.21, 1.27], 0.1512	
OR [95%-CI]; p-value	0.23 [0.07, 0.80], 0.0135		2.68 [0.31, 23.60], 0.3554		0.50 [0.19, 1.29], 0.1454	
RD [95%-CI]; p-value	-0.11 [-0.22, -0.01], 0.0341		0.03 [-0.03, 0.09], 0.2877		-0.04 [-0.10, 0.02], 0.1834	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_3_m_pt_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.4196		0.9112		0.5785	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	1/10 (10.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	1/18 (5.6)
RR [95%-CI]; p-value	0.32 [0.01, 8.75], 0.5016		0.44 [0.01, 20.20], 0.6714		0.26 [0.01, 7.41], 0.4313	
OR [95%-CI]; p-value	0.30 [0.01, 9.87], 0.4778		0.42 [0.01, 23.13], 0.6635		0.25 [0.01, 7.83], 0.3966	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.14], 0.5186		-0.03 [-0.21, 0.14], 0.7070		-0.04 [-0.15, 0.07], 0.4767	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	8/100 (8.0)	3/52 (5.8)	4/100 (4.0)	6/52 (11.5)	12/200 (6.0)	9/104 (8.7)
RR [95%-CI]; p-value	1.39 [0.38, 5.01], 0.6177		0.35 [0.10, 1.17], 0.0888		0.69 [0.30, 1.59], 0.3878	
OR [95%-CI]; p-value	1.42 [0.36, 5.60], 0.6146		0.32 [0.09, 1.19], 0.0753		0.67 [0.27, 1.66], 0.3867	
RD [95%-CI]; p-value	0.02 [-0.06, 0.11], 0.5971		-0.08 [-0.17, 0.02], 0.1197		-0.03 [-0.09, 0.04], 0.4110	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_3_m_pt_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.8.1.1.s8.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6515		0.9153		0.5825	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	1/34 (2.9)	0/18 (0.0)
RR [95%-CI]; p-value	1.40 [0.05, 38.03], 0.8417		0.44 [0.01, 20.20], 0.6714		1.09 [0.04, 30.93], 0.9605	
OR [95%-CI]; p-value	1.43 [0.04, 46.86], 0.8406		0.42 [0.01, 23.13], 0.6635		1.09 [0.03, 34.12], 0.9605	
RD [95%-CI]; p-value	0.02 [-0.16, 0.20], 0.8360		-0.03 [-0.21, 0.14], 0.7070		0.00 [-0.09, 0.10], 0.9600	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	1/52 (1.9)	2/100 (2.0)	3/52 (5.8)	3/200 (1.5)	4/104 (3.8)
RR [95%-CI]; p-value	0.52 [0.03, 8.15], 0.6413		0.35 [0.06, 2.01], 0.2374		0.39 [0.09, 1.71], 0.2118	
OR [95%-CI]; p-value	0.52 [0.03, 8.41], 0.6356		0.33 [0.05, 2.06], 0.2164		0.38 [0.08, 1.73], 0.1957	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.6675		-0.04 [-0.11, 0.03], 0.2847		-0.02 [-0.06, 0.02], 0.2576	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_8_1_1_m_soc_sae5pct_vitd_pp.sas using SAS 9.4

Table 12.4.8.1.2.s8.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_8_1_2_m_pt_sae5pct_vitd_pp.sas using SAS 9.4

Table 12.4.5.1.1.s8.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_5_1_1_m_soc_aeg35pct_vitd_pp.sas using SAS 9.4

Table 12.4.5.1.2.s8.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_5_1_2_m_pt_aeg35pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6511		0.5234		0.7846	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	3/10 (30.0)	6/19 (31.6)	2/8 (25.0)	8/34 (23.5)	5/18 (27.8)
RR [95%-CI]; p-value	0.44 [0.09, 2.20], 0.3206		1.26 [0.32, 4.97], 0.7383		0.85 [0.32, 2.21], 0.7348	
OR [95%-CI]; p-value	0.36 [0.05, 2.68], 0.3074		1.38 [0.21, 8.98], 0.7325		0.80 [0.22, 2.94], 0.7364	
RD [95%-CI]; p-value	-0.17 [-0.50, 0.17], 0.3252		0.07 [-0.30, 0.43], 0.7244		-0.04 [-0.29, 0.21], 0.7404	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	19/100 (19.0)	15/52 (28.8)	17/100 (17.0)	4/52 (7.7)	36/200 (18.0)	19/104 (18.3)
RR [95%-CI]; p-value	0.66 [0.37, 1.19], 0.1641		2.21 [0.78, 6.23], 0.1337		0.99 [0.60, 1.63], 0.9538	
OR [95%-CI]; p-value	0.58 [0.27, 1.26], 0.1670		2.46 [0.78, 7.73], 0.1146		0.98 [0.53, 1.82], 0.9539	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.05], 0.1837		0.09 [-0.01, 0.20], 0.0773		-0.00 [-0.09, 0.09], 0.9540	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.3993		0.0977		0.4155	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	1/10 (10.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	1.33 [0.14, 12.82], 0.8033		0.10 [0.01, 2.03], 0.1352		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	1.38 [0.11, 17.67], 0.8016		0.08 [0.00, 2.00], 0.0631		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	0.03 [-0.22, 0.29], 0.7965		-0.22 [-0.53, 0.08], 0.1536		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	13/100 (13.0)	14/52 (26.9)	14/100 (14.0)	5/52 (9.6)	27/200 (13.5)	19/104 (18.3)
RR [95%-CI]; p-value	0.48 [0.25, 0.95], 0.0349		1.46 [0.55, 3.82], 0.4452		0.74 [0.43, 1.26], 0.2695	
OR [95%-CI]; p-value	0.41 [0.17, 0.94], 0.0331		1.53 [0.52, 4.51], 0.4381		0.70 [0.37, 1.33], 0.2710	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0470		0.04 [-0.06, 0.15], 0.4135		-0.05 [-0.14, 0.04], 0.2886	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.8339		0.6020		0.7063	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	5/15 (33.3)	3/10 (30.0)	4/19 (21.1)	1/8 (12.5)	9/34 (26.5)	4/18 (22.2)
RR [95%-CI]; p-value	1.11 [0.34, 3.64], 0.8619		1.68 [0.22, 12.82], 0.6147		1.19 [0.43, 3.34], 0.7392	
OR [95%-CI]; p-value	1.17 [0.21, 6.56], 0.8611		1.87 [0.17, 19.93], 0.6014		1.26 [0.33, 4.85], 0.7364	
RD [95%-CI]; p-value	0.03 [-0.34, 0.40], 0.8602		0.09 [-0.21, 0.38], 0.5679		0.04 [-0.20, 0.29], 0.7315	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	26/100 (26.0)	14/52 (26.9)	24/100 (24.0)	13/52 (25.0)	50/200 (25.0)	27/104 (26.0)
RR [95%-CI]; p-value	0.97 [0.55, 1.68], 0.9022		0.96 [0.53, 1.72], 0.8914		0.96 [0.64, 1.44], 0.8546	
OR [95%-CI]; p-value	0.95 [0.45, 2.04], 0.9024		0.95 [0.44, 2.06], 0.8916		0.95 [0.55, 1.64], 0.8549	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9028		-0.01 [-0.15, 0.13], 0.8921		-0.01 [-0.11, 0.09], 0.8554	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.9193		0.9365		0.6783	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	1/10 (10.0)	2/19 (10.5)	0/8 (0.0)	4/34 (11.8)	1/18 (5.6)
RR [95%-CI]; p-value	1.33 [0.14, 12.82], 0.8033		1.79 [0.09, 35.64], 0.7030		2.12 [0.26, 17.56], 0.4870	
OR [95%-CI]; p-value	1.38 [0.11, 17.67], 0.8016		1.88 [0.08, 46.68], 0.6954		2.27 [0.23, 21.95], 0.4699	
RD [95%-CI]; p-value	0.03 [-0.22, 0.29], 0.7965		0.05 [-0.16, 0.26], 0.6646		0.06 [-0.09, 0.21], 0.4215	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	9/100 (9.0)	4/52 (7.7)	6/100 (6.0)	2/52 (3.8)	15/200 (7.5)	6/104 (5.8)
RR [95%-CI]; p-value	1.17 [0.38, 3.62], 0.7852		1.56 [0.33, 7.46], 0.5775		1.30 [0.52, 3.25], 0.5748	
OR [95%-CI]; p-value	1.19 [0.35, 4.05], 0.7845		1.60 [0.31, 8.20], 0.5726		1.32 [0.50, 3.52], 0.5724	
RD [95%-CI]; p-value	0.01 [-0.08, 0.10], 0.7796		0.02 [-0.05, 0.09], 0.5464		0.02 [-0.04, 0.08], 0.5573	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.1739		0.0566		0.8560	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	4/15 (26.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	6/34 (17.6)	4/18 (22.2)
RR [95%-CI]; p-value	2.67 [0.35, 20.51], 0.3460		0.28 [0.06, 1.37], 0.1167		0.79 [0.26, 2.46], 0.6890	
OR [95%-CI]; p-value	3.27 [0.31, 34.72], 0.3074		0.20 [0.03, 1.52], 0.0994		0.75 [0.18, 3.10], 0.6904	
RD [95%-CI]; p-value	0.17 [-0.12, 0.46], 0.2616		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.28, 0.19], 0.6977	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	9/52 (17.3)	9/100 (9.0)	2/52 (3.8)	19/200 (9.5)	11/104 (10.6)
RR [95%-CI]; p-value	0.58 [0.25, 1.33], 0.1983		2.34 [0.52, 10.44], 0.2651		0.90 [0.44, 1.82], 0.7649	
OR [95%-CI]; p-value	0.53 [0.20, 1.40], 0.1962		2.47 [0.51, 11.89], 0.2446		0.89 [0.41, 1.94], 0.7652	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2266		0.05 [-0.03, 0.13], 0.1877		-0.01 [-0.08, 0.06], 0.7686	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5539		0.7262		0.9448	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	2/10 (20.0)	3/19 (15.8)	1/8 (12.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	0.33 [0.03, 3.20], 0.3414		1.26 [0.15, 10.39], 0.8280		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	0.29 [0.02, 3.67], 0.3149		1.31 [0.12, 14.93], 0.8261		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	-0.13 [-0.41, 0.14], 0.3476		0.03 [-0.25, 0.31], 0.8190		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	22/100 (22.0)	17/52 (32.7)	18/100 (18.0)	11/52 (21.2)	40/200 (20.0)	28/104 (26.9)
RR [95%-CI]; p-value	0.67 [0.39, 1.15], 0.1482		0.85 [0.43, 1.66], 0.6373		0.74 [0.49, 1.13], 0.1662	
OR [95%-CI]; p-value	0.58 [0.27, 1.23], 0.1522		0.82 [0.35, 1.89], 0.6387		0.68 [0.39, 1.18], 0.1694	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1656		-0.03 [-0.17, 0.10], 0.6449		-0.07 [-0.17, 0.03], 0.1821	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2827		0.1594		0.0868	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	5/10 (50.0)	3/19 (15.8)	4/8 (50.0)	5/34 (14.7)	9/18 (50.0)
RR [95%-CI]; p-value	0.27 [0.06, 1.12], 0.0703		0.32 [0.09, 1.10], 0.0703		0.29 [0.12, 0.75], 0.0101	
OR [95%-CI]; p-value	0.15 [0.02, 1.07], 0.0455		0.19 [0.03, 1.20], 0.0640		0.17 [0.05, 0.65], 0.0063	
RD [95%-CI]; p-value	-0.37 [-0.72, -0.01], 0.0426		-0.34 [-0.73, 0.04], 0.0802		-0.35 [-0.61, -0.09], 0.0078	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	18/100 (18.0)	15/52 (28.8)	17/100 (17.0)	10/52 (19.2)	35/200 (17.5)	25/104 (24.0)
RR [95%-CI]; p-value	0.62 [0.34, 1.13], 0.1220		0.88 [0.44, 1.79], 0.7320		0.73 [0.46, 1.15], 0.1717	
OR [95%-CI]; p-value	0.54 [0.25, 1.19], 0.1239		0.86 [0.36, 2.04], 0.7328		0.67 [0.38, 1.20], 0.1742	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.04], 0.1408		-0.02 [-0.15, 0.11], 0.7366		-0.07 [-0.16, 0.03], 0.1890	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8607		0.0979		0.3845	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.05, 9.47], 0.7646		0.28 [0.06, 1.37], 0.1167		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.64 [0.04, 11.63], 0.7634		0.20 [0.03, 1.52], 0.0994		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.19], 0.7713		-0.27 [-0.63, 0.09], 0.1450		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	10/52 (19.2)	11/100 (11.0)	4/52 (7.7)	21/200 (10.5)	14/104 (13.5)
RR [95%-CI]; p-value	0.52 [0.23, 1.17], 0.1136		1.43 [0.48, 4.27], 0.5217		0.78 [0.41, 1.47], 0.4420	
OR [95%-CI]; p-value	0.47 [0.18, 1.21], 0.1102		1.48 [0.45, 4.91], 0.5165		0.75 [0.37, 1.55], 0.4428	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1387		0.03 [-0.06, 0.13], 0.4945		-0.03 [-0.11, 0.05], 0.4577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1844		0.5350		0.2212	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	3/10 (30.0)	4/19 (21.1)	2/8 (25.0)	5/34 (14.7)	5/18 (27.8)
RR [95%-CI]; p-value	0.22 [0.03, 1.85], 0.1638		0.84 [0.19, 3.71], 0.8203		0.53 [0.18, 1.59], 0.2572	
OR [95%-CI]; p-value	0.17 [0.01, 1.91], 0.1190		0.80 [0.11, 5.59], 0.8218		0.45 [0.11, 1.82], 0.2552	
RD [95%-CI]; p-value	-0.23 [-0.54, 0.08], 0.1412		-0.04 [-0.39, 0.31], 0.8258		-0.13 [-0.37, 0.11], 0.2832	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	14/100 (14.0)	7/52 (13.5)	9/100 (9.0)	3/52 (5.8)	23/200 (11.5)	10/104 (9.6)
RR [95%-CI]; p-value	1.04 [0.45, 2.42], 0.9274		1.56 [0.44, 5.52], 0.4901		1.20 [0.59, 2.42], 0.6181	
OR [95%-CI]; p-value	1.05 [0.39, 2.78], 0.9273		1.62 [0.42, 6.24], 0.4834		1.22 [0.56, 2.67], 0.6163	
RD [95%-CI]; p-value	0.01 [-0.11, 0.12], 0.9269		0.03 [-0.05, 0.12], 0.4543		0.02 [-0.05, 0.09], 0.6073	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4712		0.0323		0.0469	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	2/10 (20.0)	0/19 (0.0)	3/8 (37.5)	0/34 (0.0)	5/18 (27.8)
RR [95%-CI]; p-value	0.16 [0.01, 3.22], 0.2325		0.07 [0.00, 1.22], 0.0678		0.05 [0.00, 0.90], 0.0423	
OR [95%-CI]; p-value	0.13 [0.01, 3.32], 0.1643		0.04 [0.00, 1.03], 0.0125		0.04 [0.00, 0.75], 0.0031	
RD [95%-CI]; p-value	-0.17 [-0.43, 0.10], 0.2114		-0.35 [-0.69, -0.01], 0.0457		-0.26 [-0.47, -0.05], 0.0143	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	12/100 (12.0)	3/52 (5.8)	18/200 (9.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		2.08 [0.61, 7.05], 0.2394		1.04 [0.48, 2.23], 0.9199	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		2.23 [0.60, 8.28], 0.2217		1.04 [0.45, 2.41], 0.9198	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.06 [-0.03, 0.15], 0.1741		0.00 [-0.06, 0.07], 0.9194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.5594		0.9844		0.4465	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	1/10 (10.0)	1/19 (5.3)	1/8 (12.5)	1/34 (2.9)	2/18 (11.1)
RR [95%-CI]; p-value	0.32 [0.01, 8.75], 0.5016		0.42 [0.03, 5.93], 0.5217		0.26 [0.03, 2.72], 0.2638	
OR [95%-CI]; p-value	0.30 [0.01, 9.87], 0.4778		0.39 [0.02, 7.11], 0.5121		0.24 [0.02, 2.88], 0.2293	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.14], 0.5186		-0.07 [-0.32, 0.18], 0.5708		-0.08 [-0.24, 0.07], 0.3043	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	12/100 (12.0)	7/52 (13.5)	5/100 (5.0)	6/52 (11.5)	17/200 (8.5)	13/104 (12.5)
RR [95%-CI]; p-value	0.89 [0.37, 2.13], 0.7957		0.43 [0.14, 1.35], 0.1500		0.68 [0.34, 1.35], 0.2678	
OR [95%-CI]; p-value	0.88 [0.32, 2.38], 0.7960		0.40 [0.12, 1.39], 0.1399		0.65 [0.30, 1.40], 0.2673	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.10], 0.7991		-0.07 [-0.16, 0.03], 0.1854		-0.04 [-0.11, 0.03], 0.2919	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.4.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.6285		0.6892		0.7842	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	3/10 (30.0)	2/19 (10.5)	0/8 (0.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	0.11 [0.01, 1.93], 0.1300		1.79 [0.09, 35.64], 0.7030		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	0.08 [0.00, 1.77], 0.0551		1.88 [0.08, 46.68], 0.6954		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	-0.27 [-0.57, 0.03], 0.0776		0.05 [-0.16, 0.26], 0.6646		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	9/52 (17.3)	4/100 (4.0)	0/52 (0.0)	8/200 (4.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.23 [0.07, 0.71], 0.0110		4.20 [0.23, 77.94], 0.3356		0.46 [0.18, 1.16], 0.1011	
OR [95%-CI]; p-value	0.20 [0.06, 0.68], 0.0054		4.33 [0.22, 83.56], 0.2907		0.44 [0.16, 1.18], 0.0939	
RD [95%-CI]; p-value	-0.13 [-0.24, -0.02], 0.0175		0.03 [-0.02, 0.08], 0.1993		-0.05 [-0.11, 0.01], 0.1315	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_4_m_pt_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.9164		0.2643		0.3322	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	2/19 (10.5)	3/8 (37.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.28 [0.06, 1.37], 0.1167		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.20 [0.03, 1.52], 0.0994		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	9/100 (9.0)	2/52 (3.8)	4/100 (4.0)	2/52 (3.8)	13/200 (6.5)	4/104 (3.8)
RR [95%-CI]; p-value	2.34 [0.52, 10.44], 0.2651		1.04 [0.20, 5.49], 0.9632		1.69 [0.57, 5.05], 0.3478	
OR [95%-CI]; p-value	2.47 [0.51, 11.89], 0.2446		1.04 [0.18, 5.88], 0.9631		1.74 [0.55, 5.47], 0.3394	
RD [95%-CI]; p-value	0.05 [-0.03, 0.13], 0.1877		0.00 [-0.06, 0.07], 0.9629		0.03 [-0.02, 0.08], 0.3014	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8666		NA		0.7995	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	0/52 (0.0)	0/100 (0.0)	0/52 (0.0)	1/200 (0.5)	0/104 (0.0)
RR [95%-CI]; p-value	1.05 [0.04, 30.79], 0.9774		NA		1.05 [0.04, 30.89], 0.9797	
OR [95%-CI]; p-value	1.05 [0.03, 31.84], 0.9774		NA		1.05 [0.03, 31.41], 0.9797	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9772		NA		0.00 [-0.02, 0.02], 0.9795	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8622		0.2643		0.3803	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	2/19 (10.5)	3/8 (37.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.28 [0.06, 1.37], 0.1167		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.20 [0.03, 1.52], 0.0994		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	8/100 (8.0)	2/52 (3.8)	4/100 (4.0)	2/52 (3.8)	12/200 (6.0)	4/104 (3.8)
RR [95%-CI]; p-value	2.08 [0.46, 9.44], 0.3427		1.04 [0.20, 5.49], 0.9632		1.56 [0.52, 4.72], 0.4309	
OR [95%-CI]; p-value	2.17 [0.44, 10.63], 0.3271		1.04 [0.18, 5.88], 0.9631		1.60 [0.50, 5.08], 0.4250	
RD [95%-CI]; p-value	0.04 [-0.03, 0.12], 0.2749		0.00 [-0.06, 0.07], 0.9629		0.02 [-0.03, 0.07], 0.3937	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.5480		0.7361		0.4341	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	5/100 (5.0)	1/52 (1.9)	1/100 (1.0)	0/52 (0.0)	6/200 (3.0)	1/104 (1.0)
RR [95%-CI]; p-value	2.60 [0.31, 21.68], 0.3772		1.05 [0.04, 30.79], 0.9774		3.12 [0.38, 25.57], 0.2891	
OR [95%-CI]; p-value	2.68 [0.31, 23.60], 0.3554		1.05 [0.03, 31.84], 0.9774		3.19 [0.38, 26.82], 0.2609	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.2877		0.00 [-0.03, 0.03], 0.9772		0.02 [-0.01, 0.05], 0.1855	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9150		0.3270		0.3575	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	3/15 (20.0)	3/10 (30.0)	0/19 (0.0)	1/8 (12.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.17, 2.67], 0.5664		0.21 [0.01, 5.53], 0.3458		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.58 [0.09, 3.72], 0.5663		0.18 [0.01, 6.12], 0.2974		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.10 [-0.45, 0.25], 0.5741		-0.10 [-0.34, 0.14], 0.4165		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	7/100 (7.0)	6/52 (11.5)	9/100 (9.0)	4/52 (7.7)	16/200 (8.0)	10/104 (9.6)
RR [95%-CI]; p-value	0.61 [0.21, 1.71], 0.3452		1.17 [0.38, 3.62], 0.7852		0.83 [0.39, 1.77], 0.6325	
OR [95%-CI]; p-value	0.58 [0.18, 1.82], 0.3425		1.19 [0.35, 4.05], 0.7845		0.82 [0.36, 1.87], 0.6328	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3747		0.01 [-0.08, 0.10], 0.7796		-0.02 [-0.08, 0.05], 0.6415	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8666		0.7057		0.6407	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	0/52 (0.0)	2/100 (2.0)	1/52 (1.9)	3/200 (1.5)	1/104 (1.0)
RR [95%-CI]; p-value	1.05 [0.04, 30.79], 0.9774		1.04 [0.10, 11.20], 0.9742		1.56 [0.16, 14.81], 0.6986	
OR [95%-CI]; p-value	1.05 [0.03, 31.84], 0.9774		1.04 [0.09, 11.75], 0.9742		1.57 [0.16, 15.27], 0.6959	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9772		0.00 [-0.05, 0.05], 0.9740		0.01 [-0.02, 0.03], 0.6755	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7817		0.3619		0.4539	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	3/15 (20.0)	3/10 (30.0)	0/19 (0.0)	1/8 (12.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.17, 2.67], 0.5664		0.21 [0.01, 5.53], 0.3458		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.58 [0.09, 3.72], 0.5663		0.18 [0.01, 6.12], 0.2974		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.10 [-0.45, 0.25], 0.5741		-0.10 [-0.34, 0.14], 0.4165		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	8/100 (8.0)	4/52 (7.7)	14/200 (7.0)	10/104 (9.6)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		1.04 [0.33, 3.29], 0.9468		0.73 [0.34, 1.58], 0.4228	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		1.04 [0.30, 3.64], 0.9468		0.71 [0.30, 1.65], 0.4224	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.00 [-0.09, 0.09], 0.9465		-0.03 [-0.09, 0.04], 0.4428	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8956		0.5737		0.9254	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	2/34 (5.9)	0/18 (0.0)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		NA		2.18 [0.10, 45.81], 0.6169	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		NA		2.25 [0.10, 52.63], 0.6053	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		NA		0.03 [-0.08, 0.14], 0.5648	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	2/100 (2.0)	0/52 (0.0)	3/100 (3.0)	1/52 (1.9)	5/200 (2.5)	1/104 (1.0)
RR [95%-CI]; p-value	2.10 [0.10, 45.73], 0.6369		1.56 [0.17, 14.63], 0.6970		2.60 [0.31, 21.96], 0.3802	
OR [95%-CI]; p-value	2.12 [0.09, 47.93], 0.6283		1.58 [0.16, 15.55], 0.6939		2.64 [0.30, 22.91], 0.3602	
RD [95%-CI]; p-value	0.01 [-0.03, 0.05], 0.5889		0.01 [-0.04, 0.06], 0.6736		0.02 [-0.01, 0.04], 0.2923	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.6.s8.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.2418		0.8845		0.6528	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	4/10 (40.0)	7/19 (36.8)	2/8 (25.0)	8/34 (23.5)	6/18 (33.3)
RR [95%-CI]; p-value	0.17 [0.02, 1.28], 0.0852		1.47 [0.39, 5.61], 0.5697		0.71 [0.29, 1.72], 0.4436	
OR [95%-CI]; p-value	0.11 [0.01, 1.17], 0.0412		1.75 [0.27, 11.15], 0.5511		0.62 [0.17, 2.17], 0.4483	
RD [95%-CI]; p-value	-0.33 [-0.66, -0.00], 0.0469		0.12 [-0.25, 0.49], 0.5307		-0.10 [-0.36, 0.16], 0.4604	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	15/100 (15.0)	13/52 (25.0)	16/100 (16.0)	5/52 (9.6)	31/200 (15.5)	18/104 (17.3)
RR [95%-CI]; p-value	0.60 [0.31, 1.16], 0.1309		1.66 [0.65, 4.29], 0.2917		0.90 [0.53, 1.52], 0.6835	
OR [95%-CI]; p-value	0.53 [0.23, 1.22], 0.1313		1.79 [0.62, 5.20], 0.2792		0.88 [0.46, 1.66], 0.6843	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.04], 0.1523		0.06 [-0.04, 0.17], 0.2450		-0.02 [-0.11, 0.07], 0.6883	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_6_m_pt_adr_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.5637		0.9421		0.7639	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	47/58 (81.0)	30/35 (85.7)	37/59 (62.7)	19/30 (63.3)	84/117 (71.8)	49/65 (75.4)
RR [95%-CI]; p-value	0.95 [0.79, 1.14], 0.5494		0.99 [0.71, 1.39], 0.9541		0.95 [0.80, 1.14], 0.5941	
OR [95%-CI]; p-value	0.71 [0.23, 2.25], 0.5624		0.97 [0.39, 2.42], 0.9542		0.83 [0.42, 1.66], 0.6009	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.11], 0.5506		-0.01 [-0.22, 0.21], 0.9542		-0.04 [-0.17, 0.10], 0.5960	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	36/57 (63.2)	20/27 (74.1)	35/60 (58.3)	18/30 (60.0)	71/117 (60.7)	38/57 (66.7)
RR [95%-CI]; p-value	0.85 [0.63, 1.15], 0.2952		0.97 [0.68, 1.40], 0.8788		0.91 [0.72, 1.15], 0.4318	
OR [95%-CI]; p-value	0.60 [0.22, 1.66], 0.3216		0.93 [0.38, 2.28], 0.8796		0.77 [0.40, 1.50], 0.4439	
RD [95%-CI]; p-value	-0.11 [-0.32, 0.10], 0.3022		-0.02 [-0.23, 0.20], 0.8793		-0.06 [-0.21, 0.09], 0.4375	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.1951		0.9264		0.5061	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	9/58 (15.5)	5/35 (14.3)	6/59 (10.2)	1/30 (3.3)	15/117 (12.8)	6/65 (9.2)
RR [95%-CI]; p-value	1.09 [0.40, 2.98], 0.8725		3.05 [0.38, 24.20], 0.2911		1.39 [0.57, 3.41], 0.4728	
OR [95%-CI]; p-value	1.10 [0.34, 3.60], 0.8722		3.28 [0.38, 28.61], 0.2574		1.45 [0.53, 3.93], 0.4676	
RD [95%-CI]; p-value	0.01 [-0.14, 0.16], 0.8711		0.07 [-0.03, 0.17], 0.1819		0.04 [-0.06, 0.13], 0.4486	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	5/27 (18.5)	7/60 (11.7)	1/30 (3.3)	11/117 (9.4)	6/57 (10.5)
RR [95%-CI]; p-value	0.38 [0.11, 1.30], 0.1228		3.50 [0.45, 27.16], 0.2308		0.89 [0.35, 2.29], 0.8143	
OR [95%-CI]; p-value	0.33 [0.08, 1.35], 0.1115		3.83 [0.45, 32.67], 0.1903		0.88 [0.31, 2.52], 0.8146	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.05], 0.1610		0.08 [-0.02, 0.19], 0.1147		-0.01 [-0.11, 0.08], 0.8177	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.4937		0.1978		0.5504	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	3/35 (8.6)	2/59 (3.4)	1/30 (3.3)	8/117 (6.8)	4/65 (6.2)
RR [95%-CI]; p-value	1.21 [0.32, 4.52], 0.7802		1.02 [0.10, 10.77], 0.9889		1.11 [0.35, 3.55], 0.8589	
OR [95%-CI]; p-value	1.23 [0.29, 5.27], 0.7793		1.02 [0.09, 11.69], 0.9889		1.12 [0.32, 3.87], 0.8586	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7747		0.00 [-0.08, 0.08], 0.9888		0.01 [-0.07, 0.08], 0.8567	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	1/27 (3.7)	1/60 (1.7)	4/30 (13.3)	7/117 (6.0)	5/57 (8.8)
RR [95%-CI]; p-value	2.84 [0.36, 22.45], 0.3219		0.13 [0.01, 1.07], 0.0577		0.68 [0.23, 2.06], 0.4966	
OR [95%-CI]; p-value	3.06 [0.35, 26.76], 0.2907		0.11 [0.01, 1.03], 0.0227		0.66 [0.20, 2.18], 0.4956	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.2109		-0.12 [-0.24, 0.01], 0.0693		-0.03 [-0.11, 0.06], 0.5206	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.5319		0.7361		0.5025	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	11/58 (19.0)	5/35 (14.3)	6/59 (10.2)	3/30 (10.0)	17/117 (14.5)	8/65 (12.3)
RR [95%-CI]; p-value	1.33 [0.50, 3.50], 0.5671		1.02 [0.27, 3.79], 0.9800		1.18 [0.54, 2.58], 0.6781	
OR [95%-CI]; p-value	1.40 [0.44, 4.44], 0.5624		1.02 [0.24, 4.39], 0.9800		1.21 [0.49, 2.98], 0.6765	
RD [95%-CI]; p-value	0.05 [-0.11, 0.20], 0.5506		0.00 [-0.13, 0.13], 0.9799		0.02 [-0.08, 0.12], 0.6701	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	9/57 (15.8)	5/27 (18.5)	6/60 (10.0)	4/30 (13.3)	15/117 (12.8)	9/57 (15.8)
RR [95%-CI]; p-value	0.85 [0.32, 2.30], 0.7529		0.75 [0.23, 2.46], 0.6347		0.81 [0.38, 1.74], 0.5928	
OR [95%-CI]; p-value	0.83 [0.25, 2.75], 0.7539		0.72 [0.19, 2.78], 0.6353		0.78 [0.32, 1.92], 0.5940	
RD [95%-CI]; p-value	-0.03 [-0.20, 0.15], 0.7591		-0.03 [-0.18, 0.11], 0.6486		-0.03 [-0.14, 0.08], 0.6046	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.1174		0.8582		0.1272	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	3/35 (8.6)	2/59 (3.4)	0/30 (0.0)	4/117 (3.4)	3/65 (4.6)
RR [95%-CI]; p-value	0.40 [0.07, 2.29], 0.3049		2.07 [0.10, 44.46], 0.6426		0.74 [0.17, 3.21], 0.6882	
OR [95%-CI]; p-value	0.38 [0.06, 2.40], 0.2886		2.11 [0.09, 48.17], 0.6338		0.73 [0.16, 3.37], 0.6875	
RD [95%-CI]; p-value	-0.05 [-0.16, 0.05], 0.3341		0.02 [-0.05, 0.08], 0.5949		-0.01 [-0.07, 0.05], 0.6993	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	0/27 (0.0)	3/60 (5.0)	0/30 (0.0)	9/117 (7.7)	0/57 (0.0)
RR [95%-CI]; p-value	5.79 [0.34, 99.97], 0.2270		3.05 [0.16, 58.98], 0.4606		8.85 [0.52, 149.93], 0.1311	
OR [95%-CI]; p-value	6.35 [0.34, 118.08], 0.1593		3.16 [0.15, 65.12], 0.4332		9.50 [0.54, 166.85], 0.0619	
RD [95%-CI]; p-value	0.09 [-0.01, 0.18], 0.0695		0.03 [-0.04, 0.10], 0.3550		0.07 [0.01, 0.12], 0.0131	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9237		NA		0.9585	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	1/35 (2.9)	0/59 (0.0)	0/30 (0.0)	1/117 (0.9)	1/65 (1.5)
RR [95%-CI]; p-value	0.60 [0.04, 9.34], 0.7179		NA		0.56 [0.04, 8.74], 0.6758	
OR [95%-CI]; p-value	0.60 [0.04, 9.85], 0.7152		NA		0.55 [0.03, 8.97], 0.6716	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.7309		NA		-0.01 [-0.04, 0.03], 0.6956	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	0/30 (0.0)	0/117 (0.0)	0/57 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.8582		NA		0.8287	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	0/58 (0.0)	1/35 (2.9)	0/59 (0.0)	0/30 (0.0)	0/117 (0.0)	1/65 (1.5)
RR [95%-CI]; p-value	0.30 [0.01, 8.69], 0.4826		NA		0.28 [0.01, 8.13], 0.4563	
OR [95%-CI]; p-value	0.29 [0.01, 8.97], 0.4558		NA		0.27 [0.01, 8.26], 0.4252	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.04], 0.5132		NA		-0.01 [-0.04, 0.02], 0.4975	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	0/30 (0.0)	0/117 (0.0)	0/57 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.4950		0.1901		0.2469	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	41/58 (70.7)	28/35 (80.0)	31/59 (52.5)	12/30 (40.0)	72/117 (61.5)	40/65 (61.5)
RR [95%-CI]; p-value	0.88 [0.70, 1.12], 0.3007		1.31 [0.80, 2.17], 0.2859		1.00 [0.79, 1.27], 1.0000	
OR [95%-CI]; p-value	0.60 [0.22, 1.64], 0.3202		1.66 [0.68, 4.05], 0.2630		1.00 [0.54, 1.86], 1.0000	
RD [95%-CI]; p-value	-0.09 [-0.27, 0.08], 0.3022		0.13 [-0.09, 0.34], 0.2567		0.00 [-0.15, 0.15], 1.0000	
2.Baseline 25D ≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	27/57 (47.4)	17/27 (63.0)	29/60 (48.3)	17/30 (56.7)	56/117 (47.9)	34/57 (59.6)
RR [95%-CI]; p-value	0.75 [0.51, 1.12], 0.1613		0.85 [0.57, 1.28], 0.4447		0.80 [0.60, 1.07], 0.1304	
OR [95%-CI]; p-value	0.53 [0.21, 1.35], 0.1814		0.72 [0.30, 1.73], 0.4559		0.62 [0.33, 1.18], 0.1442	
RD [95%-CI]; p-value	-0.16 [-0.38, 0.07], 0.1716		-0.08 [-0.30, 0.13], 0.4533		-0.12 [-0.27, 0.04], 0.1393	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.3599		0.4677		0.8796	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	21/58 (36.2)	13/35 (37.1)	19/59 (32.2)	10/30 (33.3)	40/117 (34.2)	23/65 (35.4)
RR [95%-CI]; p-value	0.97 [0.56, 1.69], 0.9275		0.97 [0.52, 1.81], 0.9142		0.97 [0.64, 1.46], 0.8705	
OR [95%-CI]; p-value	0.96 [0.40, 2.29], 0.9277		0.95 [0.37, 2.42], 0.9144		0.95 [0.50, 1.79], 0.8708	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9277		-0.01 [-0.22, 0.20], 0.9146		-0.01 [-0.16, 0.13], 0.8711	
2.Baseline 25D ≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	17/57 (29.8)	12/27 (44.4)	17/60 (28.3)	6/30 (20.0)	34/117 (29.1)	18/57 (31.6)
RR [95%-CI]; p-value	0.67 [0.38, 1.20], 0.1777		1.42 [0.62, 3.22], 0.4057		0.92 [0.57, 1.48], 0.7319	
OR [95%-CI]; p-value	0.53 [0.21, 1.37], 0.1881		1.58 [0.55, 4.55], 0.3929		0.89 [0.45, 1.76], 0.7333	
RD [95%-CI]; p-value	-0.15 [-0.37, 0.08], 0.1966		0.08 [-0.10, 0.27], 0.3721		-0.03 [-0.17, 0.12], 0.7353	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.4937		0.1978		0.5504	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	3/35 (8.6)	2/59 (3.4)	1/30 (3.3)	8/117 (6.8)	4/65 (6.2)
RR [95%-CI]; p-value	1.21 [0.32, 4.52], 0.7802		1.02 [0.10, 10.77], 0.9889		1.11 [0.35, 3.55], 0.8589	
OR [95%-CI]; p-value	1.23 [0.29, 5.27], 0.7793		1.02 [0.09, 11.69], 0.9889		1.12 [0.32, 3.87], 0.8586	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7747		0.00 [-0.08, 0.08], 0.9888		0.01 [-0.07, 0.08], 0.8567	
2.Baseline 25D ≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	1/27 (3.7)	1/60 (1.7)	4/30 (13.3)	7/117 (6.0)	5/57 (8.8)
RR [95%-CI]; p-value	2.84 [0.36, 22.45], 0.3219		0.13 [0.01, 1.07], 0.0577		0.68 [0.23, 2.06], 0.4966	
OR [95%-CI]; p-value	3.06 [0.35, 26.76], 0.2907		0.11 [0.01, 1.03], 0.0227		0.66 [0.20, 2.18], 0.4956	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.2109		-0.12 [-0.24, 0.01], 0.0693		-0.03 [-0.11, 0.06], 0.5206	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.3222		0.5628		0.5919	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	7/35 (20.0)	5/59 (8.5)	1/30 (3.3)	9/117 (7.7)	8/65 (12.3)
RR [95%-CI]; p-value	0.34 [0.11, 1.09], 0.0707		2.54 [0.31, 20.79], 0.3842		0.63 [0.25, 1.54], 0.3076	
OR [95%-CI]; p-value	0.30 [0.08, 1.10], 0.0580		2.69 [0.30, 24.09], 0.3605		0.59 [0.22, 1.62], 0.3052	
RD [95%-CI]; p-value	-0.13 [-0.28, 0.02], 0.0821		0.05 [-0.04, 0.15], 0.2928		-0.05 [-0.14, 0.05], 0.3324	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	2/27 (7.4)	2/60 (3.3)	1/30 (3.3)	6/117 (5.1)	3/57 (5.3)
RR [95%-CI]; p-value	0.95 [0.18, 4.86], 0.9483		1.00 [0.09, 10.59], 1.0000		0.97 [0.25, 3.76], 0.9699	
OR [95%-CI]; p-value	0.94 [0.16, 5.50], 0.9483		1.00 [0.09, 11.49], 1.0000		0.97 [0.23, 4.04], 0.9699	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9488		0.00 [-0.08, 0.08], 1.0000		-0.00 [-0.07, 0.07], 0.9700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.5872		0.7461		0.6028	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	12/58 (20.7)	10/35 (28.6)	13/59 (22.0)	3/30 (10.0)	25/117 (21.4)	13/65 (20.0)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3841		2.20 [0.68, 7.14], 0.1879		1.07 [0.59, 1.94], 0.8283	
OR [95%-CI]; p-value	0.65 [0.25, 1.72], 0.3862		2.54 [0.66, 9.74], 0.1622		1.09 [0.51, 2.30], 0.8278	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3970		0.12 [-0.03, 0.27], 0.1176		0.01 [-0.11, 0.14], 0.8266	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	9/57 (15.8)	8/27 (29.6)	10/60 (16.7)	3/30 (10.0)	19/117 (16.2)	11/57 (19.3)
RR [95%-CI]; p-value	0.53 [0.23, 1.23], 0.1396		1.67 [0.50, 5.61], 0.4093		0.84 [0.43, 1.65], 0.6146	
OR [95%-CI]; p-value	0.45 [0.15, 1.33], 0.1404		1.80 [0.46, 7.10], 0.3964		0.81 [0.36, 1.84], 0.6161	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.06], 0.1675		0.07 [-0.08, 0.21], 0.3605		-0.03 [-0.15, 0.09], 0.6240	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1180		0.5170		0.3182	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	5/35 (14.3)	8/59 (13.6)	5/30 (16.7)	16/117 (13.7)	10/65 (15.4)
RR [95%-CI]; p-value	0.97 [0.34, 2.72], 0.9470		0.81 [0.29, 2.27], 0.6938		0.89 [0.43, 1.84], 0.7517	
OR [95%-CI]; p-value	0.96 [0.29, 3.21], 0.9471		0.78 [0.23, 2.64], 0.6948		0.87 [0.37, 2.05], 0.7522	
RD [95%-CI]; p-value	-0.00 [-0.15, 0.14], 0.9473		-0.03 [-0.19, 0.13], 0.7024		-0.02 [-0.12, 0.09], 0.7554	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	10/27 (37.0)	6/60 (10.0)	2/30 (6.7)	13/117 (11.1)	12/57 (21.1)
RR [95%-CI]; p-value	0.33 [0.14, 0.78], 0.0110		1.50 [0.32, 6.99], 0.6056		0.53 [0.26, 1.08], 0.0810	
OR [95%-CI]; p-value	0.24 [0.08, 0.72], 0.0084		1.56 [0.29, 8.21], 0.6004		0.47 [0.20, 1.11], 0.0793	
RD [95%-CI]; p-value	-0.25 [-0.45, -0.05], 0.0158		0.03 [-0.08, 0.15], 0.5771		-0.10 [-0.22, 0.02], 0.1050	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.0385		0.2053		0.0193	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	21/58 (36.2)	8/35 (22.9)	17/59 (28.8)	6/30 (20.0)	38/117 (32.5)	14/65 (21.5)
RR [95%-CI]; p-value	1.58 [0.79, 3.18], 0.1964		1.44 [0.63, 3.27], 0.3831		1.51 [0.89, 2.57], 0.1306	
OR [95%-CI]; p-value	1.92 [0.74, 4.97], 0.1782		1.62 [0.56, 4.66], 0.3693		1.75 [0.86, 3.55], 0.1175	
RD [95%-CI]; p-value	0.13 [-0.05, 0.32], 0.1598		0.09 [-0.10, 0.27], 0.3477		0.11 [-0.02, 0.24], 0.1019	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	10/57 (17.5)	9/27 (33.3)	11/60 (18.3)	8/30 (26.7)	21/117 (17.9)	17/57 (29.8)
RR [95%-CI]; p-value	0.53 [0.24, 1.14], 0.1047		0.69 [0.31, 1.53], 0.3576		0.60 [0.35, 1.05], 0.0732	
OR [95%-CI]; p-value	0.43 [0.15, 1.22], 0.1062		0.62 [0.22, 1.75], 0.3611		0.51 [0.25, 1.08], 0.0752	
RD [95%-CI]; p-value	-0.16 [-0.36, 0.05], 0.1281		-0.08 [-0.27, 0.10], 0.3801		-0.12 [-0.26, 0.02], 0.0908	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.3563		0.8970		0.6983	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	10/58 (17.2)	6/35 (17.1)	4/59 (6.8)	2/30 (6.7)	14/117 (12.0)	8/65 (12.3)
RR [95%-CI]; p-value	1.01 [0.40, 2.53], 0.9903		1.02 [0.20, 5.24], 0.9840		0.97 [0.43, 2.19], 0.9459	
OR [95%-CI]; p-value	1.01 [0.33, 3.06], 0.9903		1.02 [0.18, 5.90], 0.9840		0.97 [0.38, 2.45], 0.9460	
RD [95%-CI]; p-value	0.00 [-0.16, 0.16], 0.9903		0.00 [-0.11, 0.11], 0.9839		-0.00 [-0.10, 0.10], 0.9461	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	4/27 (14.8)	7/60 (11.7)	3/30 (10.0)	11/117 (9.4)	7/57 (12.3)
RR [95%-CI]; p-value	0.47 [0.13, 1.75], 0.2629		1.17 [0.32, 4.19], 0.8133		0.77 [0.31, 1.87], 0.5577	
OR [95%-CI]; p-value	0.43 [0.10, 1.89], 0.2555		1.19 [0.28, 4.97], 0.8125		0.74 [0.27, 2.03], 0.5584	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3067		0.02 [-0.12, 0.15], 0.8083		-0.03 [-0.13, 0.07], 0.5737	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.6969		0.9614		0.6539	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	16/58 (27.6)	15/35 (42.9)	12/59 (20.3)	7/30 (23.3)	28/117 (23.9)	22/65 (33.8)
RR [95%-CI]; p-value	0.64 [0.37, 1.13], 0.1270		0.87 [0.38, 1.98], 0.7433		0.71 [0.44, 1.13], 0.1474	
OR [95%-CI]; p-value	0.51 [0.21, 1.23], 0.1302		0.84 [0.29, 2.41], 0.7445		0.61 [0.32, 1.20], 0.1511	
RD [95%-CI]; p-value	-0.15 [-0.35, 0.05], 0.1351		-0.03 [-0.21, 0.15], 0.7483		-0.10 [-0.24, 0.04], 0.1609	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	4/27 (14.8)	9/60 (15.0)	5/30 (16.7)	16/117 (13.7)	9/57 (15.8)
RR [95%-CI]; p-value	0.83 [0.27, 2.59], 0.7470		0.90 [0.33, 2.45], 0.8366		0.87 [0.41, 1.84], 0.7082	
OR [95%-CI]; p-value	0.81 [0.21, 3.03], 0.7478		0.88 [0.27, 2.91], 0.8371		0.84 [0.35, 2.05], 0.7090	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.13], 0.7544		-0.02 [-0.18, 0.14], 0.8393		-0.02 [-0.13, 0.09], 0.7146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0406		0.1652		0.0129	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	13/35 (37.1)	7/59 (11.9)	8/30 (26.7)	13/117 (11.1)	21/65 (32.3)
RR [95%-CI]; p-value	0.28 [0.12, 0.67], 0.0040		0.44 [0.18, 1.11], 0.0825		0.34 [0.18, 0.64], 0.0008	
OR [95%-CI]; p-value	0.20 [0.07, 0.58], 0.0019		0.37 [0.12, 1.15], 0.0778		0.26 [0.12, 0.57], 0.0004	
RD [95%-CI]; p-value	-0.27 [-0.45, -0.09], 0.0032		-0.15 [-0.33, 0.03], 0.1040		-0.21 [-0.34, -0.08], 0.0011	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	14/57 (24.6)	7/27 (25.9)	13/60 (21.7)	6/30 (20.0)	27/117 (23.1)	13/57 (22.8)
RR [95%-CI]; p-value	0.95 [0.43, 2.07], 0.8924		1.08 [0.46, 2.57], 0.8556		1.01 [0.57, 1.81], 0.9683	
OR [95%-CI]; p-value	0.93 [0.33, 2.66], 0.8927		1.11 [0.37, 3.27], 0.8551		1.02 [0.48, 2.16], 0.9683	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.8934		0.02 [-0.16, 0.19], 0.8536		0.00 [-0.13, 0.14], 0.9683	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8678		0.5567		0.6089	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	5/35 (14.3)	9/59 (15.3)	4/30 (13.3)	13/117 (11.1)	9/65 (13.8)
RR [95%-CI]; p-value	0.48 [0.14, 1.68], 0.2520		1.14 [0.38, 3.41], 0.8092		0.80 [0.36, 1.78], 0.5870	
OR [95%-CI]; p-value	0.44 [0.11, 1.78], 0.2429		1.17 [0.33, 4.16], 0.8084		0.78 [0.31, 1.93], 0.5876	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.06], 0.2762		0.02 [-0.13, 0.17], 0.8048		-0.03 [-0.13, 0.07], 0.5972	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	6/27 (22.2)	4/60 (6.7)	3/30 (10.0)	11/117 (9.4)	9/57 (15.8)
RR [95%-CI]; p-value	0.55 [0.21, 1.49], 0.2402		0.67 [0.16, 2.79], 0.5788		0.60 [0.26, 1.35], 0.2164	
OR [95%-CI]; p-value	0.49 [0.15, 1.63], 0.2394		0.64 [0.13, 3.08], 0.5778		0.55 [0.22, 1.42], 0.2150	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2749		-0.03 [-0.16, 0.09], 0.5998		-0.06 [-0.17, 0.04], 0.2482	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.5940		0.4292		0.8928	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	5/35 (14.3)	4/59 (6.8)	1/30 (3.3)	6/117 (5.1)	6/65 (9.2)
RR [95%-CI]; p-value	0.24 [0.05, 1.18], 0.0789		2.03 [0.24, 17.40], 0.5169		0.56 [0.19, 1.65], 0.2906	
OR [95%-CI]; p-value	0.21 [0.04, 1.17], 0.0550		2.11 [0.23, 19.75], 0.5045		0.53 [0.16, 1.72], 0.2852	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.02], 0.0895		0.03 [-0.06, 0.13], 0.4568		-0.04 [-0.12, 0.04], 0.3204	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	2/27 (7.4)	1/60 (1.7)	1/30 (3.3)	3/117 (2.6)	3/57 (5.3)
RR [95%-CI]; p-value	0.47 [0.07, 3.19], 0.4422		0.50 [0.03, 7.72], 0.6196		0.49 [0.10, 2.34], 0.3689	
OR [95%-CI]; p-value	0.45 [0.06, 3.41], 0.4333		0.49 [0.03, 8.14], 0.6131		0.47 [0.09, 2.42], 0.3598	
RD [95%-CI]; p-value	-0.04 [-0.15, 0.07], 0.4862		-0.02 [-0.09, 0.06], 0.6498		-0.03 [-0.09, 0.04], 0.4133	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3941		0.1974		0.1774	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	9/58 (15.5)	5/35 (14.3)	7/59 (11.9)	1/30 (3.3)	16/117 (13.7)	6/65 (9.2)
RR [95%-CI]; p-value	1.09 [0.40, 2.98], 0.8725		3.56 [0.46, 27.61], 0.2245		1.48 [0.61, 3.60], 0.3856	
OR [95%-CI]; p-value	1.10 [0.34, 3.60], 0.8722		3.90 [0.46, 33.31], 0.1835		1.56 [0.58, 4.20], 0.3781	
RD [95%-CI]; p-value	0.01 [-0.14, 0.16], 0.8711		0.09 [-0.02, 0.19], 0.1098		0.04 [-0.05, 0.14], 0.3539	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	5/27 (18.5)	6/60 (10.0)	4/30 (13.3)	12/117 (10.3)	9/57 (15.8)
RR [95%-CI]; p-value	0.57 [0.19, 1.70], 0.3119		0.75 [0.23, 2.46], 0.6347		0.65 [0.29, 1.45], 0.2930	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3105		0.72 [0.19, 2.78], 0.6353		0.61 [0.24, 1.54], 0.2930	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3476		-0.03 [-0.18, 0.11], 0.6486		-0.06 [-0.16, 0.05], 0.3218	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0645		0.7078		0.1765	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	3/35 (8.6)	5/59 (8.5)	2/30 (6.7)	10/117 (8.5)	5/65 (7.7)
RR [95%-CI]; p-value	1.01 [0.26, 3.95], 0.9935		1.27 [0.26, 6.17], 0.7659		1.11 [0.40, 3.11], 0.8411	
OR [95%-CI]; p-value	1.01 [0.23, 4.50], 0.9935		1.30 [0.24, 7.11], 0.7646		1.12 [0.37, 3.43], 0.8408	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9934		0.02 [-0.10, 0.13], 0.7561		0.01 [-0.07, 0.09], 0.8386	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	5/27 (18.5)	7/60 (11.7)	4/30 (13.3)	8/117 (6.8)	9/57 (15.8)
RR [95%-CI]; p-value	0.09 [0.01, 0.77], 0.0277		0.88 [0.28, 2.76], 0.8196		0.43 [0.18, 1.06], 0.0678	
OR [95%-CI]; p-value	0.08 [0.01, 0.71], 0.0053		0.86 [0.23, 3.20], 0.8200		0.39 [0.14, 1.08], 0.0620	
RD [95%-CI]; p-value	-0.17 [-0.32, -0.02], 0.0289		-0.02 [-0.16, 0.13], 0.8233		-0.09 [-0.19, 0.02], 0.0951	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8663		0.7037		0.8526	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	6/35 (17.1)	4/59 (6.8)	4/30 (13.3)	12/117 (10.3)	10/65 (15.4)
RR [95%-CI]; p-value	0.80 [0.30, 2.13], 0.6610		0.51 [0.14, 1.89], 0.3132		0.67 [0.30, 1.46], 0.3098	
OR [95%-CI]; p-value	0.77 [0.24, 2.45], 0.6616		0.47 [0.11, 2.04], 0.3069		0.63 [0.26, 1.55], 0.3092	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.12], 0.6682		-0.07 [-0.20, 0.07], 0.3503		-0.05 [-0.15, 0.05], 0.3316	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	2/27 (7.4)	2/60 (3.3)	3/30 (10.0)	6/117 (5.1)	5/57 (8.8)
RR [95%-CI]; p-value	0.95 [0.18, 4.86], 0.9483		0.33 [0.06, 1.89], 0.2145		0.58 [0.19, 1.83], 0.3577	
OR [95%-CI]; p-value	0.94 [0.16, 5.50], 0.9483		0.31 [0.05, 1.97], 0.1931		0.56 [0.16, 1.93], 0.3539	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9488		-0.07 [-0.18, 0.05], 0.2623		-0.04 [-0.12, 0.05], 0.3930	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.3.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9325		0.7420		0.8120	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	7/35 (20.0)	4/59 (6.8)	0/30 (0.0)	6/117 (5.1)	7/65 (10.8)
RR [95%-CI]; p-value	0.17 [0.04, 0.78], 0.0229		4.14 [0.23, 75.71], 0.3385		0.48 [0.17, 1.36], 0.1650	
OR [95%-CI]; p-value	0.14 [0.03, 0.73], 0.0089		4.36 [0.22, 85.35], 0.2915		0.45 [0.14, 1.39], 0.1568	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0210		0.05 [-0.03, 0.13], 0.1987		-0.06 [-0.14, 0.03], 0.1949	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	5/27 (18.5)	2/60 (3.3)	0/30 (0.0)	4/117 (3.4)	5/57 (8.8)
RR [95%-CI]; p-value	0.19 [0.04, 0.91], 0.0384		2.03 [0.09, 43.72], 0.6503		0.39 [0.11, 1.40], 0.1478	
OR [95%-CI]; p-value	0.16 [0.03, 0.89], 0.0201		2.07 [0.09, 47.33], 0.6421		0.37 [0.09, 1.43], 0.1345	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0563		0.02 [-0.05, 0.08], 0.6038		-0.05 [-0.13, 0.03], 0.1924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_3_m_pt_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.3.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5323		0.7750		0.9520	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	3/58 (5.2)	5/35 (14.3)	2/59 (3.4)	0/30 (0.0)	5/117 (4.3)	5/65 (7.7)
RR [95%-CI]; p-value	0.36 [0.09, 1.42], 0.1457		2.07 [0.10, 44.46], 0.6426		0.56 [0.17, 1.85], 0.3378	
OR [95%-CI]; p-value	0.33 [0.07, 1.47], 0.1289		2.11 [0.09, 48.17], 0.6338		0.54 [0.15, 1.92], 0.3321	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.04], 0.1668		0.02 [-0.05, 0.08], 0.5949		-0.03 [-0.11, 0.04], 0.3680	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	3/27 (11.1)	5/60 (8.3)	2/30 (6.7)	6/117 (5.1)	5/57 (8.8)
RR [95%-CI]; p-value	0.16 [0.02, 1.45], 0.1026		1.25 [0.26, 6.07], 0.7820		0.58 [0.19, 1.83], 0.3577	
OR [95%-CI]; p-value	0.14 [0.01, 1.44], 0.0600		1.27 [0.23, 6.98], 0.7808		0.56 [0.16, 1.93], 0.3539	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1371		0.02 [-0.10, 0.13], 0.7733		-0.04 [-0.12, 0.05], 0.3930	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_3_m_pt_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.3.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.8606		0.7643		0.6817	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	3/35 (8.6)	3/59 (5.1)	4/30 (13.3)	9/117 (7.7)	7/65 (10.8)
RR [95%-CI]; p-value	1.21 [0.32, 4.52], 0.7802		0.38 [0.09, 1.60], 0.1867		0.71 [0.28, 1.83], 0.4830	
OR [95%-CI]; p-value	1.23 [0.29, 5.27], 0.7793		0.35 [0.07, 1.67], 0.1718		0.69 [0.24, 1.95], 0.4824	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7747		-0.08 [-0.22, 0.05], 0.2274		-0.03 [-0.12, 0.06], 0.5004	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	1/27 (3.7)	1/60 (1.7)	2/30 (6.7)	3/117 (2.6)	3/57 (5.3)
RR [95%-CI]; p-value	0.95 [0.09, 10.00], 0.9641		0.25 [0.02, 2.65], 0.2496		0.49 [0.10, 2.34], 0.3689	
OR [95%-CI]; p-value	0.95 [0.08, 10.91], 0.9641		0.24 [0.02, 2.73], 0.2129		0.47 [0.09, 2.42], 0.3598	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.08], 0.9645		-0.05 [-0.14, 0.04], 0.3021		-0.03 [-0.09, 0.04], 0.4133	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_3_m_pt_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.8.1.1.s9.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6680		0.3839		0.5221	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	0/35 (0.0)	1/59 (1.7)	3/30 (10.0)	2/117 (1.7)	3/65 (4.6)
RR [95%-CI]; p-value	1.22 [0.04, 35.56], 0.9063		0.17 [0.02, 1.56], 0.1171		0.37 [0.06, 2.16], 0.2696	
OR [95%-CI]; p-value	1.23 [0.04, 37.57], 0.9061		0.16 [0.02, 1.56], 0.0738		0.36 [0.06, 2.21], 0.2505	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9039		-0.08 [-0.20, 0.03], 0.1472		-0.03 [-0.09, 0.03], 0.3105	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	1/27 (3.7)	1/60 (1.7)	0/30 (0.0)	2/117 (1.7)	1/57 (1.8)
RR [95%-CI]; p-value	0.47 [0.03, 7.29], 0.5922		1.02 [0.04, 29.46], 0.9923		0.97 [0.09, 10.52], 0.9829	
OR [95%-CI]; p-value	0.46 [0.03, 7.72], 0.5842		1.02 [0.03, 31.18], 0.9923		0.97 [0.09, 10.97], 0.9829	
RD [95%-CI]; p-value	-0.02 [-0.10, 0.06], 0.6285		0.00 [-0.06, 0.06], 0.9923		-0.00 [-0.04, 0.04], 0.9830	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_8_1_1_m_soc_sae5pct_bl25d_pp.sas using SAS 9.4

Table 12.4.8.1.2.s9.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_8_1_2_m_pt_sae5pct_bl25d_pp.sas using SAS 9.4

Table 12.4.5.1.1.s9.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_5_1_1_m_soc_aeg35pct_bl25d_pp.sas using SAS 9.4

Table 12.4.5.1.2.s9.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_5_1_2_m_pt_aeg35pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.5872		0.7461		0.6028	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	12/58 (20.7)	10/35 (28.6)	13/59 (22.0)	3/30 (10.0)	25/117 (21.4)	13/65 (20.0)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3841		2.20 [0.68, 7.14], 0.1879		1.07 [0.59, 1.94], 0.8283	
OR [95%-CI]; p-value	0.65 [0.25, 1.72], 0.3862		2.54 [0.66, 9.74], 0.1622		1.09 [0.51, 2.30], 0.8278	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3970		0.12 [-0.03, 0.27], 0.1176		0.01 [-0.11, 0.14], 0.8266	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	9/57 (15.8)	8/27 (29.6)	10/60 (16.7)	3/30 (10.0)	19/117 (16.2)	11/57 (19.3)
RR [95%-CI]; p-value	0.53 [0.23, 1.23], 0.1396		1.67 [0.50, 5.61], 0.4093		0.84 [0.43, 1.65], 0.6146	
OR [95%-CI]; p-value	0.45 [0.15, 1.33], 0.1404		1.80 [0.46, 7.10], 0.3964		0.81 [0.36, 1.84], 0.6161	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.06], 0.1675		0.07 [-0.08, 0.21], 0.3605		-0.03 [-0.15, 0.09], 0.6240	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1180		0.5170		0.3182	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	5/35 (14.3)	8/59 (13.6)	5/30 (16.7)	16/117 (13.7)	10/65 (15.4)
RR [95%-CI]; p-value	0.97 [0.34, 2.72], 0.9470		0.81 [0.29, 2.27], 0.6938		0.89 [0.43, 1.84], 0.7517	
OR [95%-CI]; p-value	0.96 [0.29, 3.21], 0.9471		0.78 [0.23, 2.64], 0.6948		0.87 [0.37, 2.05], 0.7522	
RD [95%-CI]; p-value	-0.00 [-0.15, 0.14], 0.9473		-0.03 [-0.19, 0.13], 0.7024		-0.02 [-0.12, 0.09], 0.7554	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	10/27 (37.0)	6/60 (10.0)	2/30 (6.7)	13/117 (11.1)	12/57 (21.1)
RR [95%-CI]; p-value	0.33 [0.14, 0.78], 0.0110		1.50 [0.32, 6.99], 0.6056		0.53 [0.26, 1.08], 0.0810	
OR [95%-CI]; p-value	0.24 [0.08, 0.72], 0.0084		1.56 [0.29, 8.21], 0.6004		0.47 [0.20, 1.11], 0.0793	
RD [95%-CI]; p-value	-0.25 [-0.45, -0.05], 0.0158		0.03 [-0.08, 0.15], 0.5771		-0.10 [-0.22, 0.02], 0.1050	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.0385		0.2053		0.0193	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	21/58 (36.2)	8/35 (22.9)	17/59 (28.8)	6/30 (20.0)	38/117 (32.5)	14/65 (21.5)
RR [95%-CI]; p-value	1.58 [0.79, 3.18], 0.1964		1.44 [0.63, 3.27], 0.3831		1.51 [0.89, 2.57], 0.1306	
OR [95%-CI]; p-value	1.92 [0.74, 4.97], 0.1782		1.62 [0.56, 4.66], 0.3693		1.75 [0.86, 3.55], 0.1175	
RD [95%-CI]; p-value	0.13 [-0.05, 0.32], 0.1598		0.09 [-0.10, 0.27], 0.3477		0.11 [-0.02, 0.24], 0.1019	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	10/57 (17.5)	9/27 (33.3)	11/60 (18.3)	8/30 (26.7)	21/117 (17.9)	17/57 (29.8)
RR [95%-CI]; p-value	0.53 [0.24, 1.14], 0.1047		0.69 [0.31, 1.53], 0.3576		0.60 [0.35, 1.05], 0.0732	
OR [95%-CI]; p-value	0.43 [0.15, 1.22], 0.1062		0.62 [0.22, 1.75], 0.3611		0.51 [0.25, 1.08], 0.0752	
RD [95%-CI]; p-value	-0.16 [-0.36, 0.05], 0.1281		-0.08 [-0.27, 0.10], 0.3801		-0.12 [-0.26, 0.02], 0.0908	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.4347		0.1560		0.0865	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	4/35 (11.4)	2/59 (3.4)	2/30 (6.7)	8/117 (6.8)	6/65 (9.2)
RR [95%-CI]; p-value	0.91 [0.27, 2.99], 0.8700		0.51 [0.08, 3.43], 0.4877		0.74 [0.27, 2.04], 0.5619	
OR [95%-CI]; p-value	0.89 [0.23, 3.42], 0.8702		0.49 [0.07, 3.67], 0.4806		0.72 [0.24, 2.18], 0.5615	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8715		-0.03 [-0.13, 0.07], 0.5228		-0.02 [-0.11, 0.06], 0.5762	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	1/27 (3.7)	6/60 (10.0)	0/30 (0.0)	11/117 (9.4)	1/57 (1.8)
RR [95%-CI]; p-value	2.37 [0.29, 19.30], 0.4205		6.10 [0.35, 105.65], 0.2140		5.36 [0.71, 40.50], 0.1038	
OR [95%-CI]; p-value	2.50 [0.28, 22.52], 0.3996		6.67 [0.36, 123.52], 0.1454		5.81 [0.73, 46.17], 0.0617	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3316		0.08 [-0.00, 0.17], 0.0634		0.08 [0.01, 0.14], 0.0172	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.3563		0.8970		0.6983	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	10/58 (17.2)	6/35 (17.1)	4/59 (6.8)	2/30 (6.7)	14/117 (12.0)	8/65 (12.3)
RR [95%-CI]; p-value	1.01 [0.40, 2.53], 0.9903		1.02 [0.20, 5.24], 0.9840		0.97 [0.43, 2.19], 0.9459	
OR [95%-CI]; p-value	1.01 [0.33, 3.06], 0.9903		1.02 [0.18, 5.90], 0.9840		0.97 [0.38, 2.45], 0.9460	
RD [95%-CI]; p-value	0.00 [-0.16, 0.16], 0.9903		0.00 [-0.11, 0.11], 0.9839		-0.00 [-0.10, 0.10], 0.9461	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	4/27 (14.8)	7/60 (11.7)	3/30 (10.0)	11/117 (9.4)	7/57 (12.3)
RR [95%-CI]; p-value	0.47 [0.13, 1.75], 0.2629		1.17 [0.32, 4.19], 0.8133		0.77 [0.31, 1.87], 0.5577	
OR [95%-CI]; p-value	0.43 [0.10, 1.89], 0.2555		1.19 [0.28, 4.97], 0.8125		0.74 [0.27, 2.03], 0.5584	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3067		0.02 [-0.12, 0.15], 0.8083		-0.03 [-0.13, 0.07], 0.5737	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.6969		0.9614		0.6539	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	16/58 (27.6)	15/35 (42.9)	12/59 (20.3)	7/30 (23.3)	28/117 (23.9)	22/65 (33.8)
RR [95%-CI]; p-value	0.64 [0.37, 1.13], 0.1270		0.87 [0.38, 1.98], 0.7433		0.71 [0.44, 1.13], 0.1474	
OR [95%-CI]; p-value	0.51 [0.21, 1.23], 0.1302		0.84 [0.29, 2.41], 0.7445		0.61 [0.32, 1.20], 0.1511	
RD [95%-CI]; p-value	-0.15 [-0.35, 0.05], 0.1351		-0.03 [-0.21, 0.15], 0.7483		-0.10 [-0.24, 0.04], 0.1609	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	4/27 (14.8)	9/60 (15.0)	5/30 (16.7)	16/117 (13.7)	9/57 (15.8)
RR [95%-CI]; p-value	0.83 [0.27, 2.59], 0.7470		0.90 [0.33, 2.45], 0.8366		0.87 [0.41, 1.84], 0.7082	
OR [95%-CI]; p-value	0.81 [0.21, 3.03], 0.7478		0.88 [0.27, 2.91], 0.8371		0.84 [0.35, 2.05], 0.7090	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.13], 0.7544		-0.02 [-0.18, 0.14], 0.8393		-0.02 [-0.13, 0.09], 0.7146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0406		0.1652		0.0129	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	13/35 (37.1)	7/59 (11.9)	8/30 (26.7)	13/117 (11.1)	21/65 (32.3)
RR [95%-CI]; p-value	0.28 [0.12, 0.67], 0.0040		0.44 [0.18, 1.11], 0.0825		0.34 [0.18, 0.64], 0.0008	
OR [95%-CI]; p-value	0.20 [0.07, 0.58], 0.0019		0.37 [0.12, 1.15], 0.0778		0.26 [0.12, 0.57], 0.0004	
RD [95%-CI]; p-value	-0.27 [-0.45, -0.09], 0.0032		-0.15 [-0.33, 0.03], 0.1040		-0.21 [-0.34, -0.08], 0.0011	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	14/57 (24.6)	7/27 (25.9)	13/60 (21.7)	6/30 (20.0)	27/117 (23.1)	13/57 (22.8)
RR [95%-CI]; p-value	0.95 [0.43, 2.07], 0.8924		1.08 [0.46, 2.57], 0.8556		1.01 [0.57, 1.81], 0.9683	
OR [95%-CI]; p-value	0.93 [0.33, 2.66], 0.8927		1.11 [0.37, 3.27], 0.8551		1.02 [0.48, 2.16], 0.9683	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.8934		0.02 [-0.16, 0.19], 0.8536		0.00 [-0.13, 0.14], 0.9683	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8678		0.5567		0.6089	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	5/35 (14.3)	9/59 (15.3)	4/30 (13.3)	13/117 (11.1)	9/65 (13.8)
RR [95%-CI]; p-value	0.48 [0.14, 1.68], 0.2520		1.14 [0.38, 3.41], 0.8092		0.80 [0.36, 1.78], 0.5870	
OR [95%-CI]; p-value	0.44 [0.11, 1.78], 0.2429		1.17 [0.33, 4.16], 0.8084		0.78 [0.31, 1.93], 0.5876	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.06], 0.2762		0.02 [-0.13, 0.17], 0.8048		-0.03 [-0.13, 0.07], 0.5972	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	6/27 (22.2)	4/60 (6.7)	3/30 (10.0)	11/117 (9.4)	9/57 (15.8)
RR [95%-CI]; p-value	0.55 [0.21, 1.49], 0.2402		0.67 [0.16, 2.79], 0.5788		0.60 [0.26, 1.35], 0.2164	
OR [95%-CI]; p-value	0.49 [0.15, 1.63], 0.2394		0.64 [0.13, 3.08], 0.5778		0.55 [0.22, 1.42], 0.2150	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2749		-0.03 [-0.16, 0.09], 0.5998		-0.06 [-0.17, 0.04], 0.2482	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3941		0.1974		0.1774	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	9/58 (15.5)	5/35 (14.3)	7/59 (11.9)	1/30 (3.3)	16/117 (13.7)	6/65 (9.2)
RR [95%-CI]; p-value	1.09 [0.40, 2.98], 0.8725		3.56 [0.46, 27.61], 0.2245		1.48 [0.61, 3.60], 0.3856	
OR [95%-CI]; p-value	1.10 [0.34, 3.60], 0.8722		3.90 [0.46, 33.31], 0.1835		1.56 [0.58, 4.20], 0.3781	
RD [95%-CI]; p-value	0.01 [-0.14, 0.16], 0.8711		0.09 [-0.02, 0.19], 0.1098		0.04 [-0.05, 0.14], 0.3539	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	5/27 (18.5)	6/60 (10.0)	4/30 (13.3)	12/117 (10.3)	9/57 (15.8)
RR [95%-CI]; p-value	0.57 [0.19, 1.70], 0.3119		0.75 [0.23, 2.46], 0.6347		0.65 [0.29, 1.45], 0.2930	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3105		0.72 [0.19, 2.78], 0.6353		0.61 [0.24, 1.54], 0.2930	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3476		-0.03 [-0.18, 0.11], 0.6486		-0.06 [-0.16, 0.05], 0.3218	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0645		0.7078		0.1765	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	3/35 (8.6)	5/59 (8.5)	2/30 (6.7)	10/117 (8.5)	5/65 (7.7)
RR [95%-CI]; p-value	1.01 [0.26, 3.95], 0.9935		1.27 [0.26, 6.17], 0.7659		1.11 [0.40, 3.11], 0.8411	
OR [95%-CI]; p-value	1.01 [0.23, 4.50], 0.9935		1.30 [0.24, 7.11], 0.7646		1.12 [0.37, 3.43], 0.8408	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9934		0.02 [-0.10, 0.13], 0.7561		0.01 [-0.07, 0.09], 0.8386	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	5/27 (18.5)	7/60 (11.7)	4/30 (13.3)	8/117 (6.8)	9/57 (15.8)
RR [95%-CI]; p-value	0.09 [0.01, 0.77], 0.0277		0.88 [0.28, 2.76], 0.8196		0.43 [0.18, 1.06], 0.0678	
OR [95%-CI]; p-value	0.08 [0.01, 0.71], 0.0053		0.86 [0.23, 3.20], 0.8200		0.39 [0.14, 1.08], 0.0620	
RD [95%-CI]; p-value	-0.17 [-0.32, -0.02], 0.0289		-0.02 [-0.16, 0.13], 0.8233		-0.09 [-0.19, 0.02], 0.0951	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8663		0.7037		0.8526	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	6/35 (17.1)	4/59 (6.8)	4/30 (13.3)	12/117 (10.3)	10/65 (15.4)
RR [95%-CI]; p-value	0.80 [0.30, 2.13], 0.6610		0.51 [0.14, 1.89], 0.3132		0.67 [0.30, 1.46], 0.3098	
OR [95%-CI]; p-value	0.77 [0.24, 2.45], 0.6616		0.47 [0.11, 2.04], 0.3069		0.63 [0.26, 1.55], 0.3092	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.12], 0.6682		-0.07 [-0.20, 0.07], 0.3503		-0.05 [-0.15, 0.05], 0.3316	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	2/27 (7.4)	2/60 (3.3)	3/30 (10.0)	6/117 (5.1)	5/57 (8.8)
RR [95%-CI]; p-value	0.95 [0.18, 4.86], 0.9483		0.33 [0.06, 1.89], 0.2145		0.58 [0.19, 1.83], 0.3577	
OR [95%-CI]; p-value	0.94 [0.16, 5.50], 0.9483		0.31 [0.05, 1.97], 0.1931		0.56 [0.16, 1.93], 0.3539	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9488		-0.07 [-0.18, 0.05], 0.2623		-0.04 [-0.12, 0.05], 0.3930	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.4.s9.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT

PP Population

Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9325		0.7420		0.8120	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	7/35 (20.0)	4/59 (6.8)	0/30 (0.0)	6/117 (5.1)	7/65 (10.8)
RR [95%-CI]; p-value	0.17 [0.04, 0.78], 0.0229		4.14 [0.23, 75.71], 0.3385		0.48 [0.17, 1.36], 0.1650	
OR [95%-CI]; p-value	0.14 [0.03, 0.73], 0.0089		4.36 [0.22, 85.35], 0.2915		0.45 [0.14, 1.39], 0.1568	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0210		0.05 [-0.03, 0.13], 0.1987		-0.06 [-0.14, 0.03], 0.1949	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	5/27 (18.5)	2/60 (3.3)	0/30 (0.0)	4/117 (3.4)	5/57 (8.8)
RR [95%-CI]; p-value	0.19 [0.04, 0.91], 0.0384		2.03 [0.09, 43.72], 0.6503		0.39 [0.11, 1.40], 0.1478	
OR [95%-CI]; p-value	0.16 [0.03, 0.89], 0.0201		2.07 [0.09, 47.33], 0.6421		0.37 [0.09, 1.43], 0.1345	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0563		0.02 [-0.05, 0.08], 0.6038		-0.05 [-0.13, 0.03], 0.1924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

25 D: 25-Hydroxyvitamin D.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.

N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_4_m_pt_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.5557		0.7212		0.9649	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	2/35 (5.7)	3/59 (5.1)	2/30 (6.7)	9/117 (7.7)	4/65 (6.2)
RR [95%-CI]; p-value	1.81 [0.39, 8.48], 0.4513		0.76 [0.13, 4.32], 0.7595		1.25 [0.40, 3.90], 0.7008	
OR [95%-CI]; p-value	1.90 [0.36, 10.00], 0.4404		0.75 [0.12, 4.75], 0.7593		1.27 [0.38, 4.30], 0.6994	
RD [95%-CI]; p-value	0.05 [-0.06, 0.16], 0.4085		-0.02 [-0.12, 0.09], 0.7686		0.02 [-0.06, 0.09], 0.6907	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	0/27 (0.0)	3/60 (5.0)	3/30 (10.0)	8/117 (6.8)	3/57 (5.3)
RR [95%-CI]; p-value	4.82 [0.27, 85.20], 0.2827		0.50 [0.11, 2.33], 0.3774		1.30 [0.36, 4.71], 0.6906	
OR [95%-CI]; p-value	5.19 [0.27, 98.61], 0.2247		0.47 [0.09, 2.50], 0.3700		1.32 [0.34, 5.18], 0.6888	
RD [95%-CI]; p-value	0.07 [-0.02, 0.16], 0.1249		-0.05 [-0.17, 0.07], 0.4168		0.02 [-0.06, 0.09], 0.6760	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7205		NA		0.7536	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	0/35 (0.0)	0/59 (0.0)	0/30 (0.0)	1/117 (0.9)	0/65 (0.0)
RR [95%-CI]; p-value	1.22 [0.04, 35.56], 0.9063		NA		1.12 [0.04, 32.93], 0.9478	
OR [95%-CI]; p-value	1.23 [0.04, 37.57], 0.9061		NA		1.12 [0.04, 33.86], 0.9477	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9039		NA		0.00 [-0.03, 0.03], 0.9469	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	0/30 (0.0)	0/117 (0.0)	0/57 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4872		0.7212		0.8598	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	2/35 (5.7)	3/59 (5.1)	2/30 (6.7)	8/117 (6.8)	4/65 (6.2)
RR [95%-CI]; p-value	1.51 [0.31, 7.36], 0.6112		0.76 [0.13, 4.32], 0.7595		1.11 [0.35, 3.55], 0.8589	
OR [95%-CI]; p-value	1.56 [0.29, 8.49], 0.6068		0.75 [0.12, 4.75], 0.7593		1.12 [0.32, 3.87], 0.8586	
RD [95%-CI]; p-value	0.03 [-0.08, 0.13], 0.5892		-0.02 [-0.12, 0.09], 0.7686		0.01 [-0.07, 0.08], 0.8567	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	0/27 (0.0)	3/60 (5.0)	3/30 (10.0)	8/117 (6.8)	3/57 (5.3)
RR [95%-CI]; p-value	4.82 [0.27, 85.20], 0.2827		0.50 [0.11, 2.33], 0.3774		1.30 [0.36, 4.71], 0.6906	
OR [95%-CI]; p-value	5.19 [0.27, 98.61], 0.2247		0.47 [0.09, 2.50], 0.3700		1.32 [0.34, 5.18], 0.6888	
RD [95%-CI]; p-value	0.07 [-0.02, 0.16], 0.1249		-0.05 [-0.17, 0.07], 0.4168		0.02 [-0.06, 0.09], 0.6760	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.6507		0.7943		0.5112	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	1/35 (2.9)	0/59 (0.0)	0/30 (0.0)	2/117 (1.7)	1/65 (1.5)
RR [95%-CI]; p-value	1.21 [0.11, 12.83], 0.8761		NA		1.11 [0.10, 12.02], 0.9309	
OR [95%-CI]; p-value	1.21 [0.11, 13.90], 0.8758		NA		1.11 [0.10, 12.52], 0.9308	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8730		NA		0.00 [-0.04, 0.04], 0.9298	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	3/57 (5.3)	0/27 (0.0)	1/60 (1.7)	0/30 (0.0)	4/117 (3.4)	0/57 (0.0)
RR [95%-CI]; p-value	2.89 [0.15, 55.81], 0.4814		1.02 [0.04, 29.46], 0.9923		3.93 [0.21, 73.11], 0.3586	
OR [95%-CI]; p-value	3.00 [0.15, 62.05], 0.4565		1.02 [0.03, 31.18], 0.9923		4.04 [0.21, 77.65], 0.3180	
RD [95%-CI]; p-value	0.03 [-0.04, 0.11], 0.3775		0.00 [-0.06, 0.06], 0.9923		0.03 [-0.02, 0.07], 0.2201	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9825		0.4613		0.5759	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	5/35 (14.3)	7/59 (11.9)	3/30 (10.0)	12/117 (10.3)	8/65 (12.3)
RR [95%-CI]; p-value	0.60 [0.19, 1.94], 0.3960		1.19 [0.33, 4.26], 0.7934		0.83 [0.36, 1.93], 0.6711	
OR [95%-CI]; p-value	0.57 [0.15, 2.11], 0.3929		1.21 [0.29, 5.06], 0.7923		0.81 [0.31, 2.11], 0.6716	
RD [95%-CI]; p-value	-0.06 [-0.19, 0.08], 0.4163		0.02 [-0.12, 0.15], 0.7873		-0.02 [-0.12, 0.08], 0.6784	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	4/27 (14.8)	2/60 (3.3)	2/30 (6.7)	7/117 (6.0)	6/57 (10.5)
RR [95%-CI]; p-value	0.59 [0.17, 2.03], 0.4046		0.50 [0.07, 3.38], 0.4770		0.57 [0.20, 1.61], 0.2886	
OR [95%-CI]; p-value	0.55 [0.14, 2.25], 0.4030		0.48 [0.06, 3.61], 0.4695		0.54 [0.17, 1.69], 0.2847	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4383		-0.03 [-0.13, 0.07], 0.5142		-0.05 [-0.14, 0.05], 0.3252	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.7205		0.3614		0.2529	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	0/35 (0.0)	2/59 (3.4)	0/30 (0.0)	3/117 (2.6)	0/65 (0.0)
RR [95%-CI]; p-value	1.22 [0.04, 35.56], 0.9063		2.07 [0.10, 44.46], 0.6426		3.36 [0.17, 66.04], 0.4253	
OR [95%-CI]; p-value	1.23 [0.04, 37.57], 0.9061		2.11 [0.09, 48.17], 0.6338		3.42 [0.17, 69.36], 0.3949	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9039		0.02 [-0.05, 0.08], 0.5949		0.02 [-0.02, 0.05], 0.3210	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	1/30 (3.3)	0/117 (0.0)	1/57 (1.8)
RR [95%-CI]; p-value	NA		0.25 [0.01, 7.18], 0.4168		0.24 [0.01, 7.12], 0.4114	
OR [95%-CI]; p-value	NA		0.24 [0.01, 7.41], 0.3792		0.24 [0.01, 7.24], 0.3725	
RD [95%-CI]; p-value	NA		-0.03 [-0.09, 0.04], 0.4710		-0.01 [-0.05, 0.02], 0.4701	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.8194		0.5485		0.7735	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	5/35 (14.3)	6/59 (10.2)	3/30 (10.0)	10/117 (8.5)	8/65 (12.3)
RR [95%-CI]; p-value	0.48 [0.14, 1.68], 0.2520		1.02 [0.27, 3.79], 0.9800		0.69 [0.29, 1.67], 0.4161	
OR [95%-CI]; p-value	0.44 [0.11, 1.78], 0.2429		1.02 [0.24, 4.39], 0.9800		0.67 [0.25, 1.78], 0.4155	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.06], 0.2762		0.00 [-0.13, 0.13], 0.9799		-0.04 [-0.13, 0.06], 0.4358	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	4/27 (14.8)	2/60 (3.3)	2/30 (6.7)	7/117 (6.0)	6/57 (10.5)
RR [95%-CI]; p-value	0.59 [0.17, 2.03], 0.4046		0.50 [0.07, 3.38], 0.4770		0.57 [0.20, 1.61], 0.2886	
OR [95%-CI]; p-value	0.55 [0.14, 2.25], 0.4030		0.48 [0.06, 3.61], 0.4695		0.54 [0.17, 1.69], 0.2847	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4383		-0.03 [-0.13, 0.07], 0.5142		-0.05 [-0.14, 0.05], 0.3252	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9144		0.2694		0.3601	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	0/35 (0.0)	3/59 (5.1)	0/30 (0.0)	5/117 (4.3)	0/65 (0.0)
RR [95%-CI]; p-value	2.45 [0.11, 52.78], 0.5677		3.10 [0.16, 59.97], 0.4538		5.60 [0.31, 100.86], 0.2430	
OR [95%-CI]; p-value	2.50 [0.11, 57.05], 0.5529		3.21 [0.16, 66.30], 0.4255		5.80 [0.31, 107.94], 0.1834	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5115		0.03 [-0.04, 0.11], 0.3478		0.04 [-0.01, 0.08], 0.1037	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	0/27 (0.0)	0/60 (0.0)	1/30 (3.3)	2/117 (1.7)	1/57 (1.8)
RR [95%-CI]; p-value	1.93 [0.09, 41.38], 0.6742		0.25 [0.01, 7.18], 0.4168		0.97 [0.09, 10.52], 0.9829	
OR [95%-CI]; p-value	1.96 [0.09, 45.05], 0.6674		0.24 [0.01, 7.41], 0.3792		0.97 [0.09, 10.97], 0.9829	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.6316		-0.03 [-0.09, 0.04], 0.4710		-0.00 [-0.04, 0.04], 0.9830	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.6.s9.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.8413		0.8340		0.6374	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	9/35 (25.7)	14/59 (23.7)	4/30 (13.3)	22/117 (18.8)	13/65 (20.0)
RR [95%-CI]; p-value	0.54 [0.23, 1.26], 0.1533		1.78 [0.64, 4.94], 0.2683		0.94 [0.51, 1.74], 0.8441	
OR [95%-CI]; p-value	0.46 [0.16, 1.34], 0.1496		2.02 [0.60, 6.79], 0.2484		0.93 [0.43, 1.99], 0.8444	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1689		0.10 [-0.06, 0.27], 0.2114		-0.01 [-0.13, 0.11], 0.8454	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	8/57 (14.0)	8/27 (29.6)	9/60 (15.0)	3/30 (10.0)	17/117 (14.5)	11/57 (19.3)
RR [95%-CI]; p-value	0.47 [0.20, 1.13], 0.0910		1.50 [0.44, 5.14], 0.5185		0.75 [0.38, 1.50], 0.4196	
OR [95%-CI]; p-value	0.39 [0.13, 1.18], 0.0892		1.59 [0.40, 6.36], 0.5107		0.71 [0.31, 1.64], 0.4218	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.04], 0.1159		0.05 [-0.09, 0.19], 0.4849		-0.05 [-0.17, 0.07], 0.4388	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_6_m_pt_adr_bl25d_pp.sas using SAS 9.4

Nachberechnungsdokument Subgruppenanalysen - Wirksamkeitsendpunkte (ITT-Population)

Folgende Daten werden für die ITT-Population

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einemm 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2267		0.1472		0.0581	
Comparison Baseline vs. EAP	0.4516		0.0409		0.0461	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	150.3 (61.55)	136.7 (42.85)	163.2 (77.79)	171.4 (80.13)	156.2 (69.43)	154.6 (66.65)
Visit 13/ET						
n/N1	56/59	30/30	46/50	28/32	102/109	58/62
Mean (SD)	119.0 (65.24)	141.1 (57.39)	127.5 (113.44)	180.4 (99.16)	122.8 (89.83)	160.1 (82.02)
EAP						
n/N1	52/59	30/30	42/50	26/32	94/109	56/62
Mean (SD)	113.6 (48.64)	144.7 (59.34)	125.6 (98.74)	157.6 (74.90)	119.0 (75.04)	150.7 (66.70)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-29.0 (6.93)	1.3 (9.49)	-31.9 (11.44)	5.7 (14.69)	-31.2 (6.54)	5.2 (8.63)
95% CI	[-42.78, -15.21]	[-17.57, 20.17]	[-54.75, -9.11]	[-23.63, 34.94]	[-44.16, -18.33]	[-11.88, 22.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-30.29		-37.59		-36.41	
95% CI	[-53.72, -6.86]		[-74.80, -0.38]		[-57.80, -15.02]	
p-value	0.0119		0.0478		0.0010	
Hedges' g	-0.63		-0.48		-0.55	
95% CI	[-1.08, -0.18]		[-0.95, -0.01]		[-0.87, -0.22]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-31.9 (6.02)	5.5 (7.94)	-32.2 (9.20)	-7.3 (11.70)	-32.5 (5.39)	0.2 (6.96)
95% CI	[-43.92, -19.95]	[-10.26, 21.33]	[-50.55, -13.80]	[-30.70, 16.01]	[-43.13, -21.81]	[-13.59, 13.94]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.47		-24.83		-32.65	
95% CI	[-57.35, -17.60]		[-54.56, 4.91]		[-50.06, -15.24]	
p-value	0.0003		0.1002		0.0003	
Hedges' g	-0.87		-0.41		-0.63	
95% CI	[-1.34, -0.41]		[-0.89, 0.08]		[-0.97, -0.30]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	144.3 (51.90)	146.2 (48.43)	139.3 (54.33)	142.9 (42.08)	141.7 (53.12)	144.6 (45.19)
Visit 13/ET						
n/N2	73/82	38/42	86/94	35/40	159/176	73/82
Mean (SD)	110.5 (59.30)	154.7 (71.13)	110.2 (75.72)	161.5 (68.42)	110.3 (68.46)	157.9 (69.44)
EAP						
n/N2	65/82	34/42	82/94	35/40	147/176	69/82
Mean (SD)	106.3 (52.88)	147.4 (70.76)	106.7 (61.50)	156.6 (57.48)	106.5 (57.66)	152.1 (64.06)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.2.1.s1
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.2 (5.55)	12.5 (7.70)	-26.3 (4.89)	15.8 (7.67)	-31.1 (3.73)	14.8 (5.49)
95% CI	[-46.23, -24.21]	[-2.78, 27.75]	[-36.01, -16.64]	[0.65, 31.03]	[-38.40, -23.70]	[3.97, 25.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-47.71		-42.17		-45.84	
95% CI	[-66.54, -28.88]		[-60.20, -24.13]		[-58.92, -32.76]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.00		-0.94		-0.97	
95% CI	[-1.41, -0.59]		[-1.35, -0.53]		[-1.26, -0.68]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.1 (4.91)	8.3 (6.79)	-28.0 (4.11)	12.9 (6.30)	-32.1 (3.17)	10.6 (4.60)
95% CI	[-45.87, -26.37]	[-5.22, 21.76]	[-36.16, -19.88]	[0.38, 25.35]	[-38.33, -25.81]	[1.52, 19.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.39		-40.88		-42.67	
95% CI	[-61.04, -27.74]		[-55.81, -25.95]		[-53.69, -31.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.12		-1.08		-1.09	
95% CI	[-1.56, -0.68]		[-1.49, -0.66]		[-1.40, -0.79]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_2_1_m_pth_age.sas using SAS 9.4

Table 12.2.1.1.1.s1
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.9476		0.0667		0.0853	
Vist 13/ET	0.3766		0.0816		0.0538	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
EAP:n/N1 (%)	16/59 (27.1)	2/30 (6.7)	15/50 (30.0)	5/32 (15.6)	31/109 (28.4)	7/62 (11.3)
RR [95%-CI]; p-value	4.07 [1.00, 16.54], 0.0499		1.92 [0.77, 4.77], 0.1599		2.52 [1.18, 5.38], 0.0170	
OR [95%-CI]; p-value	5.21 [1.11, 24.42], 0.0232		2.31 [0.75, 7.16], 0.1392		3.12 [1.28, 7.60], 0.0095	
RD [95%-CI]; p-value	0.20 [0.06, 0.35], 0.0055		0.14 [-0.04, 0.32], 0.1150		0.17 [0.06, 0.29], 0.0037	
Vist 13/ET:n/N1 (%)	22/59 (37.3)	4/30 (13.3)	20/50 (40.0)	6/32 (18.8)	42/109 (38.5)	10/62 (16.1)
RR [95%-CI]; p-value	2.80 [1.06, 7.38], 0.0378		2.13 [0.96, 4.73], 0.0625		2.39 [1.29, 4.42], 0.0055	
OR [95%-CI]; p-value	3.86 [1.19, 12.55], 0.0188		2.89 [1.01, 8.28], 0.0437		3.26 [1.50, 7.10], 0.0022	
RD [95%-CI]; p-value	0.24 [0.07, 0.41], 0.0067		0.21 [0.02, 0.40], 0.0298		0.22 [0.09, 0.35], 0.0007	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
EAP:n/N2 (%)	30/82 (36.6)	4/42 (9.5)	34/94 (36.2)	0/40 (0.0)	64/176 (36.4)	4/82 (4.9)
RR [95%-CI]; p-value	3.84 [1.45, 10.18], 0.0068		29.30 [1.84, 466.48], 0.0168		7.45 [2.81, 19.77], <0.0001	
OR [95%-CI]; p-value	5.48 [1.78, 16.87], 0.0014		45.33 [2.70, 761.03], <0.0001		11.14 [3.90, 31.86], <0.0001	
RD [95%-CI]; p-value	0.27 [0.13, 0.41], 0.0001		0.35 [0.25, 0.45], <0.0001		0.31 [0.23, 0.40], <0.0001	
Vist 13/ET:n/N2 (%)	32/82 (39.0)	3/42 (7.1)	41/94 (43.6)	2/40 (5.0)	73/176 (41.5)	5/82 (6.1)
RR [95%-CI]; p-value	5.46 [1.78, 16.80], 0.0031		8.72 [2.22, 34.34], 0.0019		6.80 [2.86, 16.19], <0.0001	
OR [95%-CI]; p-value	8.32 [2.37, 29.19], 0.0002		14.70 [3.35, 64.52], <0.0001		10.91 [4.21, 28.31], <0.0001	
RD [95%-CI]; p-value	0.32 [0.19, 0.45], <0.0001		0.39 [0.27, 0.51], <0.0001		0.35 [0.26, 0.44], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_1_1_1_m_pth30pct_age.sas using SAS 9.4

Table 12.2.1.1.2.s1
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.1703		0.1485		0.0457	
Vist 13/ET	0.5271		0.5159		0.3523	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
EAP:n/N1 (%)	38/59 (64.4)	10/30 (33.3)	32/50 (64.0)	11/32 (34.4)	70/109 (64.2)	21/62 (33.9)
RR [95%-CI]; p-value	1.93 [1.13, 3.32], 0.0169		1.86 [1.10, 3.14], 0.0196		1.90 [1.30, 2.76], 0.0008	
OR [95%-CI]; p-value	3.62 [1.43, 9.15], 0.0054		3.39 [1.34, 8.61], 0.0088		3.50 [1.82, 6.75], 0.0001	
RD [95%-CI]; p-value	0.31 [0.10, 0.52], 0.0035		0.30 [0.08, 0.51], 0.0061		0.30 [0.16, 0.45], <0.0001	
Vist 13/ET:n/N1 (%)	37/59 (62.7)	9/30 (30.0)	37/50 (74.0)	11/32 (34.4)	74/109 (67.9)	20/62 (32.3)
RR [95%-CI]; p-value	2.09 [1.17, 3.74], 0.0129		2.15 [1.30, 3.57], 0.0030		2.10 [1.43, 3.09], 0.0001	
OR [95%-CI]; p-value	3.92 [1.53, 10.07], 0.0035		5.43 [2.07, 14.26], 0.0004		4.44 [2.28, 8.65], <0.0001	
RD [95%-CI]; p-value	0.33 [0.12, 0.53], 0.0018		0.40 [0.19, 0.60], 0.0001		0.36 [0.21, 0.50], <0.0001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
EAP:n/N2 (%)	49/82 (59.8)	7/42 (16.7)	58/94 (61.7)	7/40 (17.5)	107/176 (60.8)	14/82 (17.1)
RR [95%-CI]; p-value	3.59 [1.78, 7.21], 0.0003		3.53 [1.77, 7.04], 0.0004		3.56 [2.18, 5.82], <0.0001	
OR [95%-CI]; p-value	7.42 [2.95, 18.70], <0.0001		7.60 [3.04, 18.97], <0.0001		7.53 [3.93, 14.43], <0.0001	
RD [95%-CI]; p-value	0.43 [0.28, 0.59], <0.0001		0.44 [0.29, 0.60], <0.0001		0.44 [0.33, 0.55], <0.0001	
Vist 13/ET:n/N2 (%)	53/82 (64.6)	10/42 (23.8)	59/94 (62.8)	9/40 (22.5)	112/176 (63.6)	19/82 (23.2)
RR [95%-CI]; p-value	2.71 [1.54, 4.77], 0.0005		2.79 [1.54, 5.06], 0.0007		2.75 [1.82, 4.14], <0.0001	
OR [95%-CI]; p-value	5.85 [2.52, 13.58], <0.0001		5.81 [2.48, 13.61], <0.0001		5.80 [3.19, 10.55], <0.0001	
RD [95%-CI]; p-value	0.41 [0.24, 0.57], <0.0001		0.40 [0.24, 0.56], <0.0001		0.40 [0.29, 0.52], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_2_1_1_2_m_pth10pct_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9627		0.4055		0.5571	
Comparison Baseline vs. EAP	0.0600		0.2124		0.0278	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	19.2 (4.94)	19.7 (6.19)	17.9 (5.41)	18.5 (6.16)	18.6 (5.18)	19.1 (6.15)
Visit 13/ET						
n/N1	57/59	30/30	46/50	28/32	103/109	58/62
Mean (SD)	64.4 (25.19)	16.6 (6.36)	60.7 (25.34)	18.8 (6.68)	62.7 (25.20)	17.7 (6.55)
EAP						
n/N1	52/59	30/30	42/50	26/32	94/109	56/62
Mean (SD)	65.6 (25.57)	17.1 (6.05)	60.0 (21.58)	18.6 (6.77)	63.1 (23.91)	17.8 (6.38)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.2 (2.73)	-2.9 (3.77)	42.8 (3.02)	0.4 (3.88)	43.9 (2.03)	-1.3 (2.70)
95% CI	[39.73, 50.60]	[-10.41, 4.59]	[36.73, 48.77]	[-7.29, 8.17]	[39.93, 47.96]	[-6.60, 4.05]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.08		42.31		45.22	
95% CI	[38.81, 57.34]		[32.50, 52.13]		[38.54, 51.90]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.32		2.06		2.22	
95% CI	[1.76, 2.88]		[1.49, 2.63]		[1.82, 2.62]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.7 (2.86)	-2.3 (3.78)	42.4 (2.68)	0.7 (3.41)	44.6 (1.99)	-0.9 (2.57)
95% CI	[41.04, 52.45]	[-9.84, 5.19]	[37.08, 47.78]	[-6.15, 7.45]	[40.63, 48.49]	[-5.94, 4.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.07		41.78		45.42	
95% CI	[39.62, 58.52]		[33.12, 50.44]		[39.00, 51.85]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.38		2.39		2.39	
95% CI	[1.80, 2.95]		[1.76, 3.02]		[1.96, 2.81]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	20.9 (5.09)	18.9 (4.88)	20.6 (5.43)	20.1 (4.90)	20.8 (5.26)	19.5 (4.89)
Visit 13/ET						
n/N2	74/82	38/42	86/94	34/40	160/176	72/82
Mean (SD)	65.6 (24.33)	18.2 (6.03)	68.4 (23.86)	20.8 (6.70)	67.1 (24.04)	19.4 (6.45)
EAP						
n/N2	66/82	34/42	82/94	35/40	148/176	69/82
Mean (SD)	68.2 (19.37)	18.1 (6.48)	70.2 (20.61)	20.1 (6.32)	69.3 (20.03)	19.1 (6.43)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.2.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.8 (2.27)	-0.6 (3.19)	47.7 (2.16)	0.0 (3.43)	46.3 (1.56)	-0.3 (2.33)
95% CI	[40.29, 49.29]	[-6.90, 5.72]	[43.43, 51.97]	[-6.78, 6.80]	[43.18, 49.34]	[-4.91, 4.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.38		47.69		46.59	
95% CI	[37.57, 53.18]		[39.67, 55.71]		[41.05, 52.12]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.34		2.38		2.38	
95% CI	[1.84, 2.83]		[1.88, 2.88]		[2.03, 2.73]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.3 (1.87)	-0.5 (2.62)	49.5 (1.87)	-0.2 (2.87)	48.4 (1.33)	-0.4 (1.95)
95% CI	[43.59, 51.01]	[-5.72, 4.67]	[45.74, 53.17]	[-5.88, 5.49]	[45.78, 51.04]	[-4.26, 3.42]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.83		49.65		48.83	
95% CI	[41.40, 54.25]		[42.86, 56.45]		[44.17, 53.50]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.17		2.92		3.05	
95% CI	[2.57, 3.78]		[2.38, 3.46]		[2.64, 3.45]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_2_1_m_25d_age.sas using SAS 9.4

Table 12.3.1.1.s1
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4710		0.8918		0.4398	
Vist 13/ET	0.8689		0.5655		0.6865	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
EAP:n/N1 (%)	49/59 (83.1)	0/30 (0.0)	40/50 (80.0)	2/32 (6.3)	89/109 (81.7)	2/62 (3.2)
RR [95%-CI]; p-value	50.66 [3.23, 793.59], 0.0052		12.80 [3.32, 49.33], 0.0002		25.31 [6.46, 99.24], <0.0001	
OR [95%-CI]; p-value	294.00 [16.56, 5218.42], <0.0001		60.00 [12.23, 294.30], <0.0001		133.50 [30.09, 592.33], <0.0001	
RD [95%-CI]; p-value	0.81 [0.71, 0.92], <0.0001		0.74 [0.60, 0.88], <0.0001		0.78 [0.70, 0.87], <0.0001	
Vist 13/ET:n/N1 (%)	52/59 (88.1)	1/30 (3.3)	43/50 (86.0)	2/32 (6.3)	95/109 (87.2)	3/62 (4.8)
RR [95%-CI]; p-value	26.44 [3.84, 182.03], 0.0009		13.76 [3.58, 52.90], 0.0001		18.01 [5.96, 54.45], <0.0001	
OR [95%-CI]; p-value	215.43 [25.25, 1838.29], <0.0001		92.14 [17.89, 474.62], <0.0001		133.45 [36.79, 484.11], <0.0001	
RD [95%-CI]; p-value	0.85 [0.74, 0.95], <0.0001		0.80 [0.67, 0.93], <0.0001		0.82 [0.74, 0.91], <0.0001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
EAP:n/N2 (%)	64/82 (78.0)	2/42 (4.8)	80/94 (85.1)	3/40 (7.5)	144/176 (81.8)	5/82 (6.1)
RR [95%-CI]; p-value	16.39 [4.22, 63.69], <0.0001		11.35 [3.81, 33.80], <0.0001		13.42 [5.72, 31.46], <0.0001	
OR [95%-CI]; p-value	71.11 [15.66, 322.98], <0.0001		70.48 [19.08, 260.26], <0.0001		69.30 [25.95, 185.07], <0.0001	
RD [95%-CI]; p-value	0.73 [0.62, 0.84], <0.0001		0.78 [0.67, 0.88], <0.0001		0.76 [0.68, 0.83], <0.0001	
Vist 13/ET:n/N2 (%)	65/82 (79.3)	1/42 (2.4)	80/94 (85.1)	4/40 (10.0)	145/176 (82.4)	5/82 (6.1)
RR [95%-CI]; p-value	33.29 [4.79, 231.59], 0.0004		8.51 [3.35, 21.65], <0.0001		13.51 [5.76, 31.68], <0.0001	
OR [95%-CI]; p-value	156.76 [20.09, 1223.00], <0.0001		51.43 [15.82, 167.16], <0.0001		72.03 [26.92, 192.73], <0.0001	
RD [95%-CI]; p-value	0.77 [0.67, 0.87], <0.0001		0.75 [0.63, 0.87], <0.0001		0.76 [0.69, 0.84], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_3_1_1_m_25d30_age.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9342		0.1171		0.2033	
Comparison Baseline vs. EAP	0.3502		0.0506		0.0325	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	142.6 (52.18)	141.7 (50.75)	143.8 (65.03)	155.0 (69.63)	143.2 (58.75)	148.9 (61.65)
Visit 13/ET						
n/N1	64/71	32/33	65/71	32/39	129/142	64/72
Mean (SD)	108.7 (59.84)	142.6 (57.79)	99.4 (53.43)	167.4 (98.25)	104.0 (56.67)	155.0 (80.93)
EAP						
n/N1	60/71	31/33	61/71	32/39	121/142	63/72
Mean (SD)	104.6 (46.05)	147.6 (61.27)	103.5 (52.34)	159.2 (80.14)	104.0 (49.12)	153.5 (71.14)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-33.0 (5.34)	3.5 (7.55)	-41.6 (6.06)	10.8 (8.66)	-37.3 (4.03)	7.2 (5.72)
95% CI	[-43.59, -22.38]	[-11.52, 18.47]	[-53.68, -29.62]	[-6.39, 28.02]	[-45.28, -29.40]	[-4.10, 18.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-36.46		-52.46		-44.52	
95% CI	[-54.83, -18.09]		[-73.55, -31.38]		[-58.33, -30.71]	
p-value	0.0002		<0.0001		<0.0001	
Hedges' g	-0.84		-0.97		-0.91	
95% CI	[-1.28, -0.40]		[-1.41, -0.53]		[-1.23, -0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-37.8 (4.90)	8.5 (6.81)	-36.6 (4.92)	8.9 (6.81)	-37.3 (3.47)	9.0 (4.81)
95% CI	[-47.50, -28.04]	[-5.04, 22.04]	[-46.35, -26.80]	[-4.63, 22.41]	[-44.19, -30.48]	[-0.50, 18.50]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-46.27		-45.47		-46.33	
95% CI	[-62.95, -29.59]		[-62.19, -28.75]		[-58.05, -34.62]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.16		-1.07		-1.12	
95% CI	[-1.62, -0.69]		[-1.52, -0.62]		[-1.45, -0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	151.1 (59.70)	142.6 (42.48)	151.3 (63.64)	156.2 (55.43)	151.2 (61.53)	148.8 (48.96)
Visit 13/ET						
n/N2	65/70	36/39	67/73	31/33	132/143	67/72
Mean (SD)	119.6 (63.76)	154.0 (71.73)	132.4 (113.93)	172.5 (65.96)	126.1 (92.56)	162.6 (69.23)
EAP						
n/N2	57/70	33/39	63/73	29/33	120/143	62/72
Mean (SD)	114.8 (55.57)	144.7 (69.53)	122.4 (93.36)	154.6 (43.60)	118.8 (77.52)	149.3 (58.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.2.1.s2
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-32.1 (6.89)	11.3 (9.27)	-16.2 (7.90)	13.7 (11.62)	-25.2 (5.41)	14.5 (7.62)
95% CI	[-45.77, -18.44]	[-7.14, 29.65]	[-31.85, -0.50]	[-9.37, 36.75]	[-35.87, -14.52]	[-0.54, 29.52]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.36		-29.86		-39.68	
95% CI	[-66.34, -20.37]		[-57.77, -1.95]		[-58.12, -21.25]	
p-value	0.0003		0.0363		<0.0001	
Hedges' g	-0.82		-0.48		-0.63	
95% CI	[-1.24, -0.40]		[-0.91, -0.05]		[-0.93, -0.33]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-31.2 (5.96)	6.6 (7.85)	-22.8 (6.62)	-0.2 (9.76)	-27.2 (4.47)	3.6 (6.23)
95% CI	[-43.01, -19.30]	[-9.01, 22.18]	[-35.95, -9.66]	[-19.61, 19.18]	[-36.03, -18.39]	[-8.67, 15.90]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.74		-22.59		-30.82	
95% CI	[-57.37, -18.10]		[-46.04, 0.87]		[-45.95, -15.70]	
p-value	0.0002		0.0589		<0.0001	
Hedges' g	-0.85		-0.44		-0.63	
95% CI	[-1.29, -0.41]		[-0.88, 0.00]		[-0.94, -0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_2_1_m_pth_sex.sas using SAS 9.4

Table 12.2.1.1.1.s2
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4291		0.4819		0.2839	
Vist 13/ET	0.8882		0.5404		0.6074	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
EAP:n/N1 (%)	25/71 (35.2)	2/33 (6.1)	25/71 (35.2)	2/39 (5.1)	50/142 (35.2)	4/72 (5.6)
RR [95%-CI]; p-value	5.81 [1.46, 23.09], 0.0124		6.87 [1.72, 27.46], 0.0065		6.34 [2.38, 16.86], 0.0002	
OR [95%-CI]; p-value	8.42 [1.86, 38.15], 0.0016		10.05 [2.23, 45.24], 0.0005		9.24 [3.18, 26.82], <0.0001	
RD [95%-CI]; p-value	0.29 [0.15, 0.43], <0.0001		0.30 [0.17, 0.43], <0.0001		0.30 [0.20, 0.39], <0.0001	
Vist 13/ET:n/N1 (%)	27/71 (38.0)	3/33 (9.1)	34/71 (47.9)	4/39 (10.3)	61/142 (43.0)	7/72 (9.7)
RR [95%-CI]; p-value	4.18 [1.37, 12.81], 0.0122		4.67 [1.79, 12.19], 0.0016		4.42 [2.13, 9.16], <0.0001	
OR [95%-CI]; p-value	6.14 [1.71, 22.07], 0.0024		8.04 [2.59, 25.00], <0.0001		6.99 [3.00, 16.32], <0.0001	
RD [95%-CI]; p-value	0.29 [0.14, 0.44], 0.0001		0.38 [0.23, 0.53], <0.0001		0.33 [0.23, 0.44], <0.0001	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
EAP:n/N2 (%)	21/70 (30.0)	4/39 (10.3)	24/73 (32.9)	3/33 (9.1)	45/143 (31.5)	7/72 (9.7)
RR [95%-CI]; p-value	2.93 [1.08, 7.91], 0.0345		3.62 [1.17, 11.17], 0.0255		3.24 [1.54, 6.81], 0.0020	
OR [95%-CI]; p-value	3.75 [1.18, 11.89], 0.0188		4.90 [1.36, 17.68], 0.0093		4.26 [1.81, 10.03], 0.0004	
RD [95%-CI]; p-value	0.20 [0.05, 0.34], 0.0070		0.24 [0.09, 0.38], 0.0014		0.22 [0.12, 0.32], <0.0001	
Vist 13/ET:n/N2 (%)	27/70 (38.6)	4/39 (10.3)	27/73 (37.0)	4/33 (12.1)	54/143 (37.8)	8/72 (11.1)
RR [95%-CI]; p-value	3.76 [1.42, 9.96], 0.0077		3.05 [1.16, 8.02], 0.0236		3.40 [1.71, 6.75], 0.0005	
OR [95%-CI]; p-value	5.49 [1.76, 17.20], 0.0017		4.26 [1.35, 13.42], 0.0092		4.85 [2.16, 10.90], <0.0001	
RD [95%-CI]; p-value	0.28 [0.13, 0.43], 0.0002		0.25 [0.09, 0.41], 0.0019		0.27 [0.16, 0.37], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_1_1_1_m_pth30pct_sex.sas using SAS 9.4

Table 12.2.1.1.2.s2
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4569		0.4860		0.9870	
Vist 13/ET	0.4441		0.4840		0.9504	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
EAP:n/N1 (%)	47/71 (66.2)	7/33 (21.2)	49/71 (69.0)	12/39 (30.8)	96/142 (67.6)	19/72 (26.4)
RR [95%-CI]; p-value	3.12 [1.58, 6.15], 0.0010		2.24 [1.37, 3.68], 0.0014		2.56 [1.71, 3.83], <0.0001	
OR [95%-CI]; p-value	7.27 [2.76, 19.16], <0.0001		5.01 [2.15, 11.68], 0.0001		5.82 [3.10, 10.94], <0.0001	
RD [95%-CI]; p-value	0.45 [0.27, 0.63], <0.0001		0.38 [0.20, 0.56], <0.0001		0.41 [0.28, 0.54], <0.0001	
Vist 13/ET:n/N1 (%)	49/71 (69.0)	11/33 (33.3)	50/71 (70.4)	10/39 (25.6)	99/142 (69.7)	21/72 (29.2)
RR [95%-CI]; p-value	2.07 [1.25, 3.44], 0.0049		2.75 [1.58, 4.79], 0.0004		2.39 [1.64, 3.48], <0.0001	
OR [95%-CI]; p-value	4.45 [1.85, 10.75], 0.0006		6.90 [2.86, 16.67], <0.0001		5.59 [3.00, 10.41], <0.0001	
RD [95%-CI]; p-value	0.36 [0.16, 0.55], 0.0003		0.45 [0.27, 0.62], <0.0001		0.41 [0.28, 0.53], <0.0001	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
EAP:n/N2 (%)	40/70 (57.1)	10/39 (25.6)	41/73 (56.2)	6/33 (18.2)	81/143 (56.6)	16/72 (22.2)
RR [95%-CI]; p-value	2.23 [1.26, 3.95], 0.0060		3.09 [1.46, 6.55], 0.0033		2.55 [1.62, 4.02], <0.0001	
OR [95%-CI]; p-value	3.87 [1.64, 9.14], 0.0016		5.77 [2.13, 15.64], 0.0003		4.57 [2.40, 8.73], <0.0001	
RD [95%-CI]; p-value	0.32 [0.14, 0.49], 0.0006		0.38 [0.21, 0.55], <0.0001		0.34 [0.22, 0.47], <0.0001	
Vist 13/ET:n/N2 (%)	41/70 (58.6)	8/39 (20.5)	46/73 (63.0)	10/33 (30.3)	87/143 (60.8)	18/72 (25.0)
RR [95%-CI]; p-value	2.86 [1.49, 5.46], 0.0015		2.08 [1.20, 3.59], 0.0086		2.43 [1.60, 3.71], <0.0001	
OR [95%-CI]; p-value	5.48 [2.20, 13.63], 0.0001		3.92 [1.62, 9.46], 0.0018		4.66 [2.48, 8.75], <0.0001	
RD [95%-CI]; p-value	0.38 [0.21, 0.55], <0.0001		0.33 [0.14, 0.52], 0.0008		0.36 [0.23, 0.49], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_2_1_1_2_m_pth10pct_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0439		0.4164		0.0455	
Comparison Baseline vs. EAP	0.1869		0.2142		0.0706	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	20.3 (5.11)	20.0 (5.13)	19.6 (5.06)	18.6 (4.99)	20.0 (5.08)	19.2 (5.08)
Visit 13/ET						
n/N1	66/71	32/33	65/71	31/39	131/142	63/72
Mean (SD)	72.6 (23.42)	18.2 (6.56)	69.1 (24.27)	18.1 (6.08)	70.8 (23.82)	18.1 (6.28)
EAP						
n/N1	61/71	31/33	61/71	32/39	122/142	63/72
Mean (SD)	73.2 (22.17)	18.3 (6.50)	69.4 (20.80)	18.0 (6.12)	71.3 (21.49)	18.1 (6.26)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	52.6 (2.36)	-1.9 (3.39)	49.5 (2.52)	-1.1 (3.66)	51.0 (1.72)	-1.4 (2.49)
95% CI	[47.88, 57.25]	[-8.63, 4.82]	[44.49, 54.52]	[-8.36, 6.18]	[47.59, 54.39]	[-6.31, 3.50]
Diff in LS-Mean [ER-Calcifediol - Placebo]	54.46		50.59		52.39	
95% CI	[46.27, 62.66]		[41.75, 59.44]		[46.42, 58.37]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.84		2.43		2.64	
95% CI	[2.26, 3.41]		[1.88, 2.97]		[2.24, 3.04]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	53.7 (2.26)	-1.7 (3.17)	49.9 (2.16)	-0.7 (2.98)	51.8 (1.56)	-1.1 (2.17)
95% CI	[49.16, 58.15]	[-7.99, 4.62]	[45.66, 54.22]	[-6.58, 5.26]	[48.69, 54.84]	[-5.39, 3.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	55.34		50.60		52.88	
95% CI	[47.60, 63.09]		[43.28, 57.92]		[47.60, 58.15]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.12		2.99		3.07	
95% CI	[2.50, 3.74]		[2.38, 3.59]		[2.64, 3.51]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	20.1 (5.08)	18.6 (5.66)	19.7 (6.04)	20.3 (6.00)	19.9 (5.57)	19.4 (5.84)
Visit 13/ET						
n/N2	65/70	36/39	67/73	31/33	132/143	67/72
Mean (SD)	57.5 (23.62)	16.9 (5.86)	62.4 (24.60)	21.6 (6.95)	60.0 (24.15)	19.1 (6.76)
EAP						
n/N2	57/70	33/39	63/73	29/33	120/143	62/72
Mean (SD)	60.4 (20.52)	17.1 (6.05)	64.2 (21.85)	21.0 (6.65)	62.4 (21.22)	18.9 (6.60)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.2.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	37.5 (2.35)	-1.8 (3.17)	42.9 (2.43)	0.7 (3.57)	40.1 (1.68)	-0.4 (2.37)
95% CI	[32.79, 42.12]	[-8.06, 4.52]	[38.11, 47.74]	[-6.39, 7.80]	[36.80, 43.43]	[-5.07, 4.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	39.22		42.22		40.52	
95% CI	[31.35, 47.09]		[33.62, 50.81]		[34.79, 46.24]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.05		2.12		2.10	
95% CI	[1.56, 2.55]		[1.60, 2.63]		[1.74, 2.45]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	40.4 (2.17)	-1.8 (2.85)	44.4 (2.22)	0.8 (3.28)	42.4 (1.55)	-0.4 (2.16)
95% CI	[36.10, 44.71]	[-7.46, 3.89]	[40.00, 48.83]	[-5.68, 7.34]	[39.31, 45.43]	[-4.67, 3.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.20		43.59		42.78	
95% CI	[35.04, 49.35]		[35.72, 51.46]		[37.54, 48.03]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.55		2.46		2.53	
95% CI	[1.99, 3.12]		[1.90, 3.03]		[2.12, 2.93]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_2_1_m_25d_sex.sas using SAS 9.4

Table 12.3.1.1.s2
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3294		0.1489		0.6681	
Vist 13/ET	0.3396		0.0894		0.4257	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
EAP:n/N1 (%)	58/71 (81.7)	2/33 (6.1)	60/71 (84.5)	1/39 (2.6)	118/142 (83.1)	3/72 (4.2)
RR [95%-CI]; p-value	13.48 [3.50, 51.88], 0.0002		32.96 [4.75, 228.71], 0.0004		19.94 [6.57, 60.53], <0.0001	
OR [95%-CI]; p-value	69.15 [14.66, 326.22], <0.0001		207.27 [25.71, 1670.85], <0.0001		113.08 [32.84, 389.38], <0.0001	
RD [95%-CI]; p-value	0.76 [0.63, 0.88], <0.0001		0.82 [0.72, 0.92], <0.0001		0.79 [0.71, 0.87], <0.0001	
Vist 13/ET:n/N1 (%)	61/71 (85.9)	2/33 (6.1)	62/71 (87.3)	1/39 (2.6)	123/142 (86.6)	3/72 (4.2)
RR [95%-CI]; p-value	14.18 [3.69, 54.49], 0.0001		34.06 [4.91, 236.21], 0.0004		20.79 [6.85, 63.06], <0.0001	
OR [95%-CI]; p-value	94.55 [19.50, 458.36], <0.0001		261.78 [31.89, 2148.60], <0.0001		148.89 [42.54, 521.16], <0.0001	
RD [95%-CI]; p-value	0.80 [0.68, 0.91], <0.0001		0.85 [0.76, 0.94], <0.0001		0.82 [0.75, 0.90], <0.0001	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
EAP:n/N2 (%)	55/70 (78.6)	0/39 (0.0)	60/73 (82.2)	4/33 (12.1)	115/143 (80.4)	4/72 (5.6)
RR [95%-CI]; p-value	62.07 [3.94, 977.71], 0.0033		6.78 [2.69, 17.10], <0.0001		14.48 [5.57, 37.65], <0.0001	
OR [95%-CI]; p-value	286.00 [16.59, 4931.18], <0.0001		33.46 [10.03, 111.67], <0.0001		69.82 [23.48, 207.61], <0.0001	
RD [95%-CI]; p-value	0.77 [0.67, 0.88], <0.0001		0.70 [0.56, 0.84], <0.0001		0.75 [0.66, 0.83], <0.0001	
Vist 13/ET:n/N2 (%)	56/70 (80.0)	0/39 (0.0)	61/73 (83.6)	5/33 (15.2)	117/143 (81.8)	5/72 (6.9)
RR [95%-CI]; p-value	63.20 [4.01, 995.26], 0.0032		5.52 [2.44, 12.44], <0.0001		11.78 [5.04, 27.54], <0.0001	
OR [95%-CI]; p-value	312.00 [18.04, 5395.59], <0.0001		28.47 [9.15, 88.58], <0.0001		60.30 [22.11, 164.42], <0.0001	
RD [95%-CI]; p-value	0.79 [0.69, 0.89], <0.0001		0.68 [0.54, 0.83], <0.0001		0.75 [0.66, 0.84], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_3_1_1_m_25d30_sex.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5995		0.4874		0.4043	
Comparison Baseline vs. EAP	0.1686		0.0534		0.0148	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	147.0 (59.64)	140.1 (45.67)	150.3 (69.42)	171.5 (79.25)	148.7 (64.65)	154.1 (64.32)
Visit 13/ET						
n/N1	66/73	33/36	71/77	26/29	137/150	59/65
Mean (SD)	111.6 (64.45)	140.2 (48.90)	119.0 (93.91)	186.0 (89.16)	115.5 (80.86)	160.4 (72.62)
EAP						
n/N1	60/73	31/36	64/77	25/29	124/150	56/65
Mean (SD)	105.1 (48.83)	137.1 (52.48)	112.3 (72.47)	174.2 (85.50)	108.8 (62.02)	153.7 (70.98)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.2 (5.66)	4.3 (8.02)	-32.6 (6.82)	12.8 (11.32)	-34.7 (4.48)	10.3 (6.87)
95% CI	[-46.45, -24.00]	[-11.59, 20.26]	[-46.19, -19.11]	[-9.68, 35.26]	[-43.51, -25.84]	[-3.28, 23.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-39.56		-45.44		-44.95	
95% CI	[-59.12, -20.00]		[-71.76, -19.11]		[-61.13, -28.76]	
p-value	0.0001		0.0009		<0.0001	
Hedges' g	-0.91		-0.78		-0.84	
95% CI	[-1.34, -0.47]		[-1.24, -0.32]		[-1.15, -0.52]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-38.6 (4.76)	5.5 (6.65)	-36.9 (4.83)	8.1 (7.75)	-38.2 (3.40)	7.8 (5.08)
95% CI	[-48.04, -29.14]	[-7.69, 18.72]	[-46.46, -27.25]	[-7.30, 23.53]	[-44.87, -31.46]	[-2.24, 17.82]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.11		-44.97		-45.96	
95% CI	[-60.45, -27.77]		[-63.18, -26.76]		[-58.02, -33.90]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.25		-1.08		-1.17	
95% CI	[-1.71, -0.78]		[-1.57, -0.60]		[-1.51, -0.84]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	146.6 (52.26)	144.3 (47.10)	144.5 (58.02)	144.8 (47.39)	145.6 (55.00)	144.6 (46.95)
Visit 13/ET						
n/N2	63/68	35/36	61/67	37/43	124/135	72/79
Mean (SD)	116.9 (59.40)	156.7 (77.59)	112.9 (87.26)	158.6 (78.16)	114.9 (74.14)	157.7 (77.34)
EAP						
n/N2	57/68	33/36	60/67	36/43	117/135	69/79
Mean (SD)	114.3 (53.11)	154.6 (74.99)	114.0 (80.78)	145.1 (42.98)	114.1 (68.42)	149.6 (60.17)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.2.1.s3
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-29.7 (6.71)	10.7 (9.00)	-22.9 (7.86)	9.8 (10.10)	-26.8 (5.23)	11.1 (6.86)
95% CI	[-43.07, -16.42]	[-7.17, 28.57]	[-38.53, -7.33]	[-10.22, 29.90]	[-37.14, -16.51]	[-2.46, 24.62]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.44		-32.78		-37.90	
95% CI	[-62.74, -18.15]		[-58.26, -7.29]		[-54.93, -20.87]	
p-value	0.0005		0.0123		<0.0001	
Hedges' g	-0.74		-0.56		-0.65	
95% CI	[-1.17, -0.32]		[-0.97, -0.15]		[-0.95, -0.36]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.6 (6.12)	8.2 (8.05)	-21.6 (6.78)	1.8 (8.76)	-25.7 (4.59)	5.2 (5.99)
95% CI	[-41.79, -17.46]	[-7.75, 24.24]	[-35.09, -8.16]	[-15.63, 19.18]	[-34.79, -16.67]	[-6.62, 17.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.87		-23.40		-30.92	
95% CI	[-57.97, -17.77]		[-45.44, -1.36]		[-45.82, -16.02]	
p-value	0.0003		0.0377		<0.0001	
Hedges' g	-0.80		-0.45		-0.61	
95% CI	[-1.24, -0.36]		[-0.87, -0.04]		[-0.91, -0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_2_1_m_pth_wt.sas using SAS 9.4

Table 12.2.1.1.1.s3
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2214		0.9324		0.3574	
Vist 13/ET	0.2317		0.7714		0.2801	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
EAP:n/N1 (%)	28/73 (38.4)	2/36 (5.6)	27/77 (35.1)	2/29 (6.9)	55/150 (36.7)	4/65 (6.2)
RR [95%-CI]; p-value	6.90 [1.74, 27.39], 0.0060		5.08 [1.29, 20.04], 0.0201		5.96 [2.25, 15.76], 0.0003	
OR [95%-CI]; p-value	10.58 [2.36, 47.51], 0.0003		7.29 [1.61, 33.02], 0.0037		8.83 [3.04, 25.60], <0.0001	
RD [95%-CI]; p-value	0.33 [0.19, 0.46], <0.0001		0.28 [0.14, 0.42], <0.0001		0.31 [0.21, 0.40], <0.0001	
Vist 13/ET:n/N1 (%)	29/73 (39.7)	2/36 (5.6)	34/77 (44.2)	3/29 (10.3)	63/150 (42.0)	5/65 (7.7)
RR [95%-CI]; p-value	7.15 [1.81, 28.31], 0.0051		4.27 [1.42, 12.83], 0.0097		5.46 [2.30, 12.94], 0.0001	
OR [95%-CI]; p-value	11.20 [2.50, 50.27], 0.0002		6.85 [1.91, 24.57], 0.0011		8.69 [3.30, 22.88], <0.0001	
RD [95%-CI]; p-value	0.34 [0.21, 0.48], <0.0001		0.34 [0.18, 0.49], <0.0001		0.34 [0.24, 0.45], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
EAP:n/N2 (%)	18/68 (26.5)	4/36 (11.1)	22/67 (32.8)	3/43 (7.0)	40/135 (29.6)	7/79 (8.9)
RR [95%-CI]; p-value	2.38 [0.87, 6.51], 0.0906		4.71 [1.50, 14.77], 0.0080		3.34 [1.57, 7.10], 0.0017	
OR [95%-CI]; p-value	2.88 [0.89, 9.29], 0.0681		6.52 [1.81, 23.43], 0.0016		4.33 [1.83, 10.23], 0.0004	
RD [95%-CI]; p-value	0.15 [0.01, 0.30], 0.0402		0.26 [0.12, 0.39], 0.0002		0.21 [0.11, 0.31], <0.0001	
Vist 13/ET:n/N2 (%)	25/68 (36.8)	5/36 (13.9)	27/67 (40.3)	5/43 (11.6)	52/135 (38.5)	10/79 (12.7)
RR [95%-CI]; p-value	2.65 [1.11, 6.33], 0.0285		3.47 [1.45, 8.31], 0.0053		3.04 [1.64, 5.64], 0.0004	
OR [95%-CI]; p-value	3.60 [1.24, 10.46], 0.0143		5.13 [1.79, 14.70], 0.0012		4.32 [2.05, 9.14], <0.0001	
RD [95%-CI]; p-value	0.23 [0.07, 0.39], 0.0053		0.29 [0.14, 0.44], 0.0002		0.26 [0.15, 0.37], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_1_1_1_m_pth30pct_wt.sas using SAS 9.4

Table 12.2.1.1.2.s3
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.7162		0.8248		0.6665	
Vist 13/ET	0.9178		0.6146		0.7647	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
EAP:n/N1 (%)	46/73 (63.0)	8/36 (22.2)	49/77 (63.6)	7/29 (24.1)	95/150 (63.3)	15/65 (23.1)
RR [95%-CI]; p-value	2.84 [1.50, 5.36], 0.0013		2.64 [1.35, 5.14], 0.0044		2.74 [1.73, 4.35], <0.0001	
OR [95%-CI]; p-value	5.96 [2.38, 14.94], <0.0001		5.50 [2.09, 14.49], 0.0003		5.76 [2.96, 11.20], <0.0001	
RD [95%-CI]; p-value	0.41 [0.23, 0.58], <0.0001		0.39 [0.21, 0.58], <0.0001		0.40 [0.27, 0.53], <0.0001	
Vist 13/ET:n/N1 (%)	48/73 (65.8)	10/36 (27.8)	51/77 (66.2)	7/29 (24.1)	99/150 (66.0)	17/65 (26.2)
RR [95%-CI]; p-value	2.37 [1.36, 4.11], 0.0022		2.74 [1.41, 5.33], 0.0029		2.52 [1.65, 3.86], <0.0001	
OR [95%-CI]; p-value	4.99 [2.08, 11.97], 0.0002		6.16 [2.33, 16.31], 0.0001		5.48 [2.87, 10.48], <0.0001	
RD [95%-CI]; p-value	0.38 [0.20, 0.56], <0.0001		0.42 [0.23, 0.61], <0.0001		0.40 [0.27, 0.53], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
EAP:n/N2 (%)	41/68 (60.3)	9/36 (25.0)	41/67 (61.2)	11/43 (25.6)	82/135 (60.7)	20/79 (25.3)
RR [95%-CI]; p-value	2.41 [1.33, 4.38], 0.0039		2.39 [1.39, 4.12], 0.0017		2.40 [1.60, 3.59], <0.0001	
OR [95%-CI]; p-value	4.56 [1.86, 11.17], 0.0006		4.59 [1.97, 10.66], 0.0003		4.56 [2.47, 8.43], <0.0001	
RD [95%-CI]; p-value	0.35 [0.17, 0.54], 0.0002		0.36 [0.18, 0.53], <0.0001		0.35 [0.23, 0.48], <0.0001	
Vist 13/ET:n/N2 (%)	42/68 (61.8)	9/36 (25.0)	45/67 (67.2)	13/43 (30.2)	87/135 (64.4)	22/79 (27.8)
RR [95%-CI]; p-value	2.47 [1.36, 4.48], 0.0029		2.22 [1.37, 3.60], 0.0012		2.31 [1.59, 3.37], <0.0001	
OR [95%-CI]; p-value	4.85 [1.97, 11.91], 0.0004		4.72 [2.06, 10.79], 0.0002		4.70 [2.56, 8.60], <0.0001	
RD [95%-CI]; p-value	0.37 [0.19, 0.55], <0.0001		0.37 [0.19, 0.55], <0.0001		0.37 [0.24, 0.49], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_2_1_1_2_m_pth10pct_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2314		0.4087		0.7792	
Comparison Baseline vs. EAP	0.8262		0.4435		0.5014	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	20.2 (5.14)	20.3 (5.36)	20.4 (5.79)	19.6 (6.37)	20.3 (5.47)	20.0 (5.80)
Visit 13/ET						
n/N1	67/73	33/36	71/77	25/29	138/150	58/65
Mean (SD)	69.2 (24.13)	18.3 (5.75)	68.4 (26.09)	20.8 (6.84)	68.8 (25.07)	19.4 (6.32)
EAP						
n/N1	60/73	31/36	64/77	25/29	124/150	56/65
Mean (SD)	72.3 (24.21)	18.7 (6.11)	70.8 (22.70)	20.6 (7.28)	71.5 (23.36)	19.5 (6.66)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.2 (2.41)	-2.1 (3.44)	48.2 (2.65)	0.8 (4.46)	48.7 (1.79)	-0.6 (2.78)
95% CI	[44.39, 53.97]	[-8.88, 4.77]	[42.93, 53.44]	[-8.08, 9.64]	[45.16, 52.21]	[-6.14, 4.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.23		47.41		49.33	
95% CI	[42.89, 59.57]		[37.10, 57.71]		[42.81, 55.86]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.59		2.12		2.36	
95% CI	[2.04, 3.13]		[1.57, 2.66]		[1.98, 2.75]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	52.5 (2.52)	-2.1 (3.52)	50.4 (2.39)	0.9 (3.82)	51.4 (1.73)	-0.6 (2.59)
95% CI	[47.47, 57.51]	[-9.06, 4.91]	[45.62, 55.11]	[-6.68, 8.51]	[48.01, 54.84]	[-5.67, 4.54]
Diff in LS-Mean [ER-Calcifediol - Placebo]	54.56		49.45		51.99	
95% CI	[45.94, 63.18]		[40.49, 58.41]		[45.85, 58.13]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.79		2.58		2.71	
95% CI	[2.20, 3.38]		[1.98, 3.17]		[2.29, 3.13]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	20.3 (5.05)	18.2 (5.37)	18.8 (5.20)	19.2 (4.93)	19.5 (5.16)	18.7 (5.13)
Visit 13/ET						
n/N2	64/68	35/36	61/67	37/43	125/135	72/79
Mean (SD)	60.8 (24.57)	16.8 (6.57)	62.6 (22.48)	19.2 (6.65)	61.7 (23.50)	18.1 (6.68)
EAP						
n/N2	58/68	33/36	60/67	36/43	118/135	69/79
Mean (SD)	61.6 (18.74)	16.7 (6.33)	62.5 (19.23)	18.7 (5.89)	62.1 (18.91)	17.7 (6.14)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.2.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	40.7 (2.47)	-1.4 (3.36)	43.5 (2.30)	-0.3 (2.96)	42.1 (1.68)	-1.0 (2.22)
95% CI	[35.76, 45.57]	[-8.11, 5.22]	[38.92, 48.07]	[-6.21, 5.54]	[38.82, 45.46]	[-5.37, 3.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.11		43.83		43.14	
95% CI	[33.77, 50.45]		[36.38, 51.28]		[37.64, 48.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.13		2.44		2.29	
95% CI	[1.63, 2.64]		[1.91, 2.97]		[1.92, 2.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	41.8 (1.96)	-1.3 (2.61)	43.6 (1.95)	-0.5 (2.52)	42.7 (1.38)	-0.9 (1.80)
95% CI	[37.87, 45.65]	[-6.46, 3.91]	[39.75, 47.51]	[-5.48, 4.54]	[40.00, 45.43]	[-4.47, 2.65]
Diff in LS-Mean [ER-Calcifediol - Placebo]	43.04		44.10		43.62	
95% CI	[36.50, 49.58]		[37.76, 50.44]		[39.14, 48.11]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.88		2.90		2.92	
95% CI	[2.29, 3.48]		[2.32, 3.48]		[2.50, 3.33]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_2_1_m_25d_wt.sas using SAS 9.4

Table 12.3.1.1.s3
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.9292		0.0848		0.1359	
Vist 13/ET	0.3761		0.5927		0.3183	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
EAP:n/N1 (%)	55/73 (75.3)	1/36 (2.8)	61/77 (79.2)	4/29 (13.8)	116/150 (77.3)	5/65 (7.7)
RR [95%-CI]; p-value	27.12 [3.91, 188.18], 0.0008		5.74 [2.30, 14.37], 0.0002		10.05 [4.31, 23.44], <0.0001	
OR [95%-CI]; p-value	106.94 [13.66, 837.23], <0.0001		23.83 [7.25, 78.36], <0.0001		40.94 [15.23, 110.09], <0.0001	
RD [95%-CI]; p-value	0.73 [0.61, 0.84], <0.0001		0.65 [0.50, 0.81], <0.0001		0.70 [0.60, 0.79], <0.0001	
Vist 13/ET:n/N1 (%)	61/73 (83.6)	2/36 (5.6)	65/77 (84.4)	3/29 (10.3)	126/150 (84.0)	5/65 (7.7)
RR [95%-CI]; p-value	15.04 [3.90, 58.06], <0.0001		8.16 [2.78, 23.93], 0.0001		10.92 [4.69, 25.42], <0.0001	
OR [95%-CI]; p-value	86.42 [18.26, 409.03], <0.0001		46.94 [12.24, 180.08], <0.0001		63.00 [22.91, 173.21], <0.0001	
RD [95%-CI]; p-value	0.78 [0.67, 0.89], <0.0001		0.74 [0.60, 0.88], <0.0001		0.76 [0.68, 0.85], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
EAP:n/N2 (%)	58/68 (85.3)	1/36 (2.8)	59/67 (88.1)	1/43 (2.3)	117/135 (86.7)	2/79 (2.5)
RR [95%-CI]; p-value	30.71 [4.43, 212.62], 0.0005		37.87 [5.45, 263.25], 0.0002		34.23 [8.70, 134.70], <0.0001	
OR [95%-CI]; p-value	203.00 [24.91, 1654.42], <0.0001		309.75 [37.32, 2570.73], <0.0001		250.25 [56.46, 1109.18], <0.0001	
RD [95%-CI]; p-value	0.83 [0.73, 0.93], <0.0001		0.86 [0.77, 0.95], <0.0001		0.84 [0.77, 0.91], <0.0001	
Vist 13/ET:n/N2 (%)	56/68 (82.4)	0/36 (0.0)	58/67 (86.6)	3/43 (7.0)	114/135 (84.4)	3/79 (3.8)
RR [95%-CI]; p-value	60.12 [3.82, 945.07], 0.0036		12.41 [4.15, 37.11], <0.0001		22.24 [7.31, 67.63], <0.0001	
OR [95%-CI]; p-value	336.00 [19.25, 5865.78], <0.0001		85.93 [21.89, 337.25], <0.0001		137.52 [39.64, 477.16], <0.0001	
RD [95%-CI]; p-value	0.81 [0.71, 0.91], <0.0001		0.80 [0.68, 0.91], <0.0001		0.81 [0.73, 0.88], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_3_1_1_m_25d30_wt.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6281		0.3976		0.4270	
Comparison Baseline vs. EAP	0.5565		0.4896		0.8714	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	144.8 (56.27)	139.1 (47.48)	142.4 (55.45)	142.2 (39.00)	143.5 (55.69)	140.6 (43.33)
Visit 13/ET						
n/N1	77/85	45/48	91/98	40/46	168/183	85/94
Mean (SD)	109.1 (59.00)	145.0 (57.89)	107.8 (84.29)	155.5 (64.34)	108.4 (73.58)	149.9 (60.87)
EAP						
n/N1	67/85	42/48	87/98	39/46	154/183	81/94
Mean (SD)	102.2 (48.51)	133.1 (49.75)	105.4 (73.69)	148.2 (45.88)	104.0 (63.80)	140.4 (48.22)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.2 (5.29)	6.4 (6.93)	-33.7 (6.47)	13.1 (9.75)	-34.7 (4.28)	10.1 (6.00)
95% CI	[-45.69, -24.73]	[-7.35, 20.10]	[-46.46, -20.87]	[-6.21, 32.38]	[-43.09, -26.25]	[-1.68, 21.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-41.58		-46.75		-44.81	
95% CI	[-58.88, -24.29]		[-69.90, -23.59]		[-59.33, -30.29]	
p-value	<0.0001		0.0001		<0.0001	
Hedges' g	-0.89		-0.76		-0.81	
95% CI	[-1.27, -0.51]		[-1.14, -0.37]		[-1.08, -0.54]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.9 (4.54)	0.3 (5.74)	-33.1 (5.19)	5.0 (7.75)	-34.2 (3.54)	2.9 (4.85)
95% CI	[-43.94, -25.94]	[-11.03, 11.72]	[-43.39, -22.84]	[-10.31, 20.39]	[-41.19, -27.23]	[-6.61, 12.49]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.28		-38.15		-37.16	
95% CI	[-49.80, -20.76]		[-56.63, -19.68]		[-48.99, -25.33]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.95		-0.77		-0.84	
95% CI	[-1.35, -0.54]		[-1.16, -0.38]		[-1.12, -0.56]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	150.0 (55.96)	148.4 (43.57)	158.7 (79.32)	179.1 (87.52)	153.9 (67.29)	164.4 (70.99)
Visit 13/ET						
n/N2	52/56	23/24	41/46	23/26	93/102	46/50
Mean (SD)	121.8 (65.68)	155.8 (78.81)	134.8 (101.91)	195.0 (105.73)	127.5 (83.36)	175.4 (94.31)
EAP						
n/N2	50/56	22/24	37/46	22/26	87/102	44/50
Mean (SD)	119.4 (52.95)	170.9 (83.20)	131.1 (80.24)	172.7 (88.43)	124.4 (65.78)	171.8 (84.86)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.2.1.s4
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-28.9 (7.52)	10.6 (11.31)	-15.6 (8.47)	7.0 (11.37)	-23.0 (5.70)	10.2 (8.06)
95% CI	[-43.83, -13.87]	[-11.94, 33.14]	[-32.57, 1.30]	[-15.76, 29.73]	[-34.24, -11.71]	[-5.77, 26.09]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-39.45		-22.62		-33.13	
95% CI	[-66.53, -12.37]		[-51.25, 6.01]		[-52.69, -13.58]	
p-value	0.0049		0.1194		0.0010	
Hedges' g	-0.74		-0.48		-0.63	
95% CI	[-1.24, -0.24]		[-0.99, 0.03]		[-0.99, -0.27]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-33.9 (6.67)	20.9 (10.05)	-20.9 (6.99)	3.1 (9.08)	-27.6 (4.90)	12.5 (6.81)
95% CI	[-47.19, -20.59]	[0.86, 40.97]	[-34.91, -6.91]	[-15.08, 21.30]	[-37.32, -17.93]	[-0.96, 26.00]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-54.80		-24.02		-40.14	
95% CI	[-78.87, -30.73]		[-47.05, -0.99]		[-56.76, -23.53]	
p-value	<0.0001		0.0412		<0.0001	
Hedges' g	-1.15		-0.54		-0.88	
95% CI	[-1.68, -0.61]		[-1.07, -0.01]		[-1.25, -0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_2_1_m_pth_race.sas using SAS 9.4

Table 12.2.1.1.1.s4
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2890		0.0677		0.6790	
Vist 13/ET	0.2563		0.8817		0.4242	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
EAP:n/N1 (%)	25/85 (29.4)	5/48 (10.4)	40/98 (40.8)	2/46 (4.3)	65/183 (35.5)	7/94 (7.4)
RR [95%-CI]; p-value	2.82 [1.16, 6.89], 0.0227		9.39 [2.37, 37.18], 0.0014		4.77 [2.28, 9.99], <0.0001	
OR [95%-CI]; p-value	3.58 [1.27, 10.11], 0.0118		15.17 [3.48, 66.20], <0.0001		6.85 [2.99, 15.66], <0.0001	
RD [95%-CI]; p-value	0.19 [0.06, 0.32], 0.0041		0.36 [0.25, 0.48], <0.0001		0.28 [0.19, 0.37], <0.0001	
Vist 13/ET:n/N1 (%)	31/85 (36.5)	6/48 (12.5)	49/98 (50.0)	6/46 (13.0)	80/183 (43.7)	12/94 (12.8)
RR [95%-CI]; p-value	2.92 [1.31, 6.49], 0.0087		3.83 [1.77, 8.30], 0.0006		3.42 [1.97, 5.96], <0.0001	
OR [95%-CI]; p-value	4.02 [1.53, 10.52], 0.0030		6.67 [2.59, 17.15], <0.0001		5.31 [2.71, 10.40], <0.0001	
RD [95%-CI]; p-value	0.24 [0.10, 0.38], 0.0007		0.37 [0.23, 0.51], <0.0001		0.31 [0.21, 0.41], <0.0001	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
EAP:n/N2 (%)	21/56 (37.5)	1/24 (4.2)	9/46 (19.6)	3/26 (11.5)	30/102 (29.4)	4/50 (8.0)
RR [95%-CI]; p-value	9.00 [1.28, 63.15], 0.0271		1.70 [0.50, 5.71], 0.3943		3.68 [1.37, 9.86], 0.0097	
OR [95%-CI]; p-value	13.80 [1.73, 109.79], 0.0022		1.86 [0.46, 7.61], 0.3800		4.79 [1.58, 14.49], 0.0029	
RD [95%-CI]; p-value	0.33 [0.18, 0.48], <0.0001		0.08 [-0.09, 0.25], 0.3490		0.21 [0.10, 0.33], 0.0003	
Vist 13/ET:n/N2 (%)	23/56 (41.1)	1/24 (4.2)	12/46 (26.1)	2/26 (7.7)	35/102 (34.3)	3/50 (6.0)
RR [95%-CI]; p-value	9.86 [1.41, 68.88], 0.0211		3.39 [0.82, 14.00], 0.0913		5.72 [1.85, 17.69], 0.0025	
OR [95%-CI]; p-value	16.03 [2.02, 127.25], 0.0010		4.24 [0.87, 20.68], 0.0582		8.18 [2.38, 28.19], 0.0002	
RD [95%-CI]; p-value	0.37 [0.22, 0.52], <0.0001		0.18 [0.02, 0.35], 0.0270		0.28 [0.17, 0.40], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_1_1_1_m_pth30pct_race.sas using SAS 9.4

Table 12.2.1.1.2.s4
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3403		0.0574		0.5560	
Vist 13/ET	0.9189		0.6621		0.8166	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
EAP:n/N1 (%)	52/85 (61.2)	13/48 (27.1)	70/98 (71.4)	10/46 (21.7)	122/183 (66.7)	23/94 (24.5)
RR [95%-CI]; p-value	2.26 [1.38, 3.70], 0.0012		3.29 [1.87, 5.77], <0.0001		2.72 [1.88, 3.94], <0.0001	
OR [95%-CI]; p-value	4.24 [1.96, 9.18], 0.0002		9.00 [3.94, 20.57], <0.0001		6.17 [3.52, 10.83], <0.0001	
RD [95%-CI]; p-value	0.34 [0.18, 0.50], <0.0001		0.50 [0.35, 0.65], <0.0001		0.42 [0.31, 0.53], <0.0001	
Vist 13/ET:n/N1 (%)	55/85 (64.7)	13/48 (27.1)	70/98 (71.4)	13/46 (28.3)	125/183 (68.3)	26/94 (27.7)
RR [95%-CI]; p-value	2.39 [1.46, 3.90], 0.0005		2.53 [1.57, 4.07], 0.0001		2.47 [1.76, 3.47], <0.0001	
OR [95%-CI]; p-value	4.94 [2.27, 10.73], <0.0001		6.35 [2.92, 13.80], <0.0001		5.64 [3.26, 9.76], <0.0001	
RD [95%-CI]; p-value	0.38 [0.21, 0.54], <0.0001		0.43 [0.27, 0.59], <0.0001		0.41 [0.29, 0.52], <0.0001	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
EAP:n/N2 (%)	35/56 (62.5)	4/24 (16.7)	20/46 (43.5)	8/26 (30.8)	55/102 (53.9)	12/50 (24.0)
RR [95%-CI]; p-value	3.75 [1.50, 9.38], 0.0047		1.41 [0.73, 2.75], 0.3075		2.25 [1.33, 3.80], 0.0025	
OR [95%-CI]; p-value	8.33 [2.50, 27.73], 0.0002		1.73 [0.63, 4.78], 0.2880		3.71 [1.74, 7.90], 0.0005	
RD [95%-CI]; p-value	0.46 [0.26, 0.65], <0.0001		0.13 [-0.10, 0.36], 0.2747		0.30 [0.15, 0.45], 0.0001	
Vist 13/ET:n/N2 (%)	35/56 (62.5)	6/24 (25.0)	26/46 (56.5)	7/26 (26.9)	61/102 (59.8)	13/50 (26.0)
RR [95%-CI]; p-value	2.50 [1.21, 5.15], 0.0129		2.10 [1.06, 4.15], 0.0331		2.30 [1.40, 3.77], 0.0009	
OR [95%-CI]; p-value	5.00 [1.71, 14.59], 0.0021		3.53 [1.24, 10.03], 0.0155		4.23 [2.01, 8.93], <0.0001	
RD [95%-CI]; p-value	0.38 [0.16, 0.59], 0.0006		0.30 [0.07, 0.52], 0.0092		0.34 [0.18, 0.49], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_2_1_1_2_m_pth10pct_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6507		0.6821		0.5744	
Comparison Baseline vs. EAP	0.0506		0.7088		0.0930	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	21.2 (4.66)	19.8 (5.42)	20.2 (5.32)	19.9 (5.51)	20.7 (5.03)	19.9 (5.43)
Visit 13/ET						
n/N1	78/85	45/48	91/98	40/46	169/183	85/94
Mean (SD)	65.1 (23.41)	17.8 (6.14)	68.0 (25.00)	20.6 (6.96)	66.6 (24.25)	19.1 (6.66)
EAP						
n/N1	67/85	42/48	87/98	39/46	154/183	81/94
Mean (SD)	68.2 (19.57)	17.9 (6.21)	68.8 (21.63)	20.5 (6.71)	68.5 (20.69)	19.2 (6.54)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.3 (2.15)	-2.5 (2.84)	47.8 (2.14)	0.4 (3.23)	45.9 (1.53)	-0.9 (2.15)
95% CI	[40.03, 48.56]	[-8.10, 3.15]	[43.53, 52.00]	[-5.98, 6.79]	[42.94, 48.95]	[-5.13, 3.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.77		47.36		46.84	
95% CI	[39.69, 53.85]		[39.69, 55.02]		[41.64, 52.03]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.40		2.31		2.37	
95% CI	[1.93, 2.87]		[1.85, 2.78]		[2.04, 2.70]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.6 (1.91)	-2.1 (2.41)	48.5 (1.87)	0.3 (2.79)	48.0 (1.35)	-0.8 (1.85)
95% CI	[43.80, 51.36]	[-6.89, 2.67]	[44.76, 52.16]	[-5.20, 5.85]	[45.31, 50.64]	[-4.47, 2.82]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.69		48.13		48.80	
95% CI	[43.58, 55.79]		[41.48, 54.78]		[44.29, 53.32]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.14		2.75		2.95	
95% CI	[2.57, 3.70]		[2.25, 3.26]		[2.57, 3.32]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	18.7 (5.35)	18.1 (5.41)	18.4 (5.91)	18.4 (5.49)	18.6 (5.58)	18.3 (5.40)
Visit 13/ET						
n/N2	53/56	23/24	41/46	22/26	94/102	45/50
Mean (SD)	65.2 (26.52)	17.0 (6.39)	60.7 (23.08)	18.5 (6.16)	63.2 (25.05)	17.8 (6.25)
EAP						
n/N2	51/56	22/24	37/46	22/26	88/102	44/50
Mean (SD)	65.5 (25.49)	17.1 (6.45)	62.0 (20.39)	17.6 (5.83)	64.0 (23.42)	17.4 (6.08)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.2.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.3 (2.90)	-0.9 (4.41)	42.0 (3.00)	-0.2 (4.09)	44.3 (2.14)	-0.9 (3.07)
95% CI	[40.55, 52.13]	[-9.68, 7.90]	[36.04, 48.03]	[-8.40, 7.98]	[40.11, 48.57]	[-6.92, 5.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.22		42.24		45.19	
95% CI	[36.69, 57.75]		[32.08, 52.40]		[37.79, 52.58]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.22		2.15		2.21	
95% CI	[1.62, 2.82]		[1.51, 2.78]		[1.77, 2.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.8 (2.90)	-1.0 (4.42)	44.0 (2.73)	-0.3 (3.54)	45.4 (2.06)	-0.7 (2.88)
95% CI	[41.01, 52.59]	[-9.78, 7.85]	[38.49, 49.42]	[-7.43, 6.74]	[41.32, 49.47]	[-6.41, 4.98]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.76		44.30		46.11	
95% CI	[37.22, 58.31]		[35.36, 53.24]		[39.10, 53.11]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.30		2.59		2.43	
95% CI	[1.68, 2.92]		[1.89, 3.29]		[1.97, 2.90]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_2_1_m_25d_race.sas using SAS 9.4

Table 12.3.1.1.s4
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.6590		0.2814		0.2960	
Vist 13/ET	0.6557		0.3941		0.2391	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
EAP:n/N1 (%)	66/85 (77.6)	1/48 (2.1)	86/98 (87.8)	5/46 (10.9)	152/183 (83.1)	6/94 (6.4)
RR [95%-CI]; p-value	37.27 [5.34, 260.08], 0.0003		8.07 [3.52, 18.53], <0.0001		13.01 [5.98, 28.30], <0.0001	
OR [95%-CI]; p-value	163.26 [21.12, 1262.37], <0.0001		58.77 [19.41, 177.89], <0.0001		71.91 [28.87, 179.15], <0.0001	
RD [95%-CI]; p-value	0.76 [0.66, 0.85], <0.0001		0.77 [0.66, 0.88], <0.0001		0.77 [0.69, 0.84], <0.0001	
Vist 13/ET:n/N1 (%)	71/85 (83.5)	2/48 (4.2)	87/98 (88.8)	5/46 (10.9)	158/183 (86.3)	7/94 (7.4)
RR [95%-CI]; p-value	20.05 [5.15, 78.11], <0.0001		8.17 [3.56, 18.74], <0.0001		11.59 [5.67, 23.70], <0.0001	
OR [95%-CI]; p-value	116.64 [25.32, 537.24], <0.0001		64.85 [21.15, 198.86], <0.0001		78.55 [32.65, 189.00], <0.0001	
RD [95%-CI]; p-value	0.79 [0.70, 0.89], <0.0001		0.78 [0.67, 0.89], <0.0001		0.79 [0.72, 0.86], <0.0001	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
EAP:n/N2 (%)	47/56 (83.9)	1/24 (4.2)	34/46 (73.9)	0/26 (0.0)	81/102 (79.4)	1/50 (2.0)
RR [95%-CI]; p-value	20.14 [2.95, 137.68], 0.0022		39.17 [2.50, 613.33], 0.0090		39.71 [5.69, 277.07], 0.0002	
OR [95%-CI]; p-value	120.11 [14.34, 1006.01], <0.0001		147.33 [8.31, 2610.70], <0.0001		189.00 [24.64, 1449.47], <0.0001	
RD [95%-CI]; p-value	0.80 [0.67, 0.92], <0.0001		0.72 [0.58, 0.86], <0.0001		0.77 [0.69, 0.86], <0.0001	
Vist 13/ET:n/N2 (%)	46/56 (82.1)	0/24 (0.0)	36/46 (78.3)	1/26 (3.8)	82/102 (80.4)	1/50 (2.0)
RR [95%-CI]; p-value	40.25 [2.58, 627.16], 0.0084		20.35 [2.96, 139.90], 0.0022		40.20 [5.76, 280.45], 0.0002	
OR [95%-CI]; p-value	220.80 [12.36, 3944.49], <0.0001		90.00 [10.82, 748.31], <0.0001		200.90 [26.14, 1543.97], <0.0001	
RD [95%-CI]; p-value	0.80 [0.69, 0.92], <0.0001		0.74 [0.60, 0.88], <0.0001		0.78 [0.70, 0.87], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_3_1_1_m_25d30_race.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2904		0.8202		0.6735	
Comparison Baseline vs. EAP	0.1478		0.7728		0.5467	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	125.1 (38.50)	127.3 (33.29)	132.1 (38.72)	141.1 (55.98)	128.8 (38.65)	134.1 (46.09)
Visit 13/ET						
n/N1	62/71	35/36	72/80	29/35	134/151	64/71
Mean (SD)	100.3 (41.98)	136.9 (68.41)	98.8 (41.46)	139.1 (75.73)	99.5 (41.55)	137.9 (71.24)
EAP						
n/N1	58/71	33/36	69/80	30/35	127/151	63/71
Mean (SD)	95.8 (38.63)	133.4 (65.28)	98.3 (35.09)	138.6 (63.49)	97.2 (36.62)	135.9 (63.97)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-24.3 (6.02)	9.5 (8.02)	-30.4 (4.06)	-3.7 (6.43)	-27.5 (3.60)	3.2 (5.24)
95% CI	[-36.30, -12.38]	[-6.46, 25.40]	[-38.46, -22.34]	[-16.43, 9.09]	[-34.59, -20.38]	[-7.09, 13.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-33.81		-26.73		-30.72	
95% CI	[-53.74, -13.87]		[-41.89, -11.57]		[-43.29, -18.16]	
p-value	0.0011		0.0007		<0.0001	
Hedges' g	-0.65		-0.74		-0.70	
95% CI	[-1.08, -0.23]		[-1.18, -0.30]		[-1.01, -0.40]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.0 (5.57)	6.0 (7.38)	-30.0 (3.31)	-4.6 (5.06)	-29.6 (3.16)	0.9 (4.48)
95% CI	[-40.07, -17.94]	[-8.69, 20.65]	[-36.58, -23.42]	[-14.66, 5.43]	[-35.86, -23.40]	[-7.95, 9.74]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-34.98		-25.38		-30.52	
95% CI	[-53.37, -16.60]		[-37.48, -13.28]		[-41.38, -19.67]	
p-value	0.0003		<0.0001		<0.0001	
Hedges' g	-0.77		-0.80		-0.78	
95% CI	[-1.21, -0.33]		[-1.24, -0.36]		[-1.09, -0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	168.9 (62.30)	157.1 (52.45)	167.0 (82.39)	169.2 (67.06)	168.0 (72.32)	163.2 (60.19)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	127.1 (73.74)	161.2 (60.39)	137.1 (123.87)	196.2 (81.38)	131.8 (100.29)	178.9 (73.43)
EAP						
n/N2	59/70	31/36	55/64	31/37	114/134	62/73
Mean (SD)	123.1 (57.89)	159.7 (63.25)	131.7 (105.23)	174.9 (62.08)	127.2 (83.85)	167.3 (62.62)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.2.1.s5
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-41.0 (6.32)	7.4 (9.04)	-26.4 (9.99)	25.2 (13.28)	-34.3 (5.84)	17.5 (8.03)
95% CI	[-53.58, -28.48]	[-10.52, 25.37]	[-46.23, -6.54]	[-1.13, 51.61]	[-45.81, -22.77]	[1.65, 33.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-48.45		-51.62		-51.78	
95% CI	[-70.45, -26.45]		[-84.64, -18.61]		[-71.38, -32.19]	
p-value	<0.0001		0.0025		<0.0001	
Hedges' g	-0.98		-0.67		-0.80	
95% CI	[-1.42, -0.55]		[-1.10, -0.24]		[-1.10, -0.49]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-40.3 (5.38)	9.6 (7.44)	-29.4 (8.28)	14.0 (11.03)	-35.0 (4.88)	12.2 (6.61)
95% CI	[-50.94, -29.57]	[-5.15, 24.43]	[-45.84, -12.91]	[-7.93, 35.94]	[-44.63, -25.39]	[-0.85, 25.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-49.89		-43.38		-47.21	
95% CI	[-68.23, -31.56]		[-70.81, -15.95]		[-63.44, -30.98]	
p-value	<0.0001		0.0023		<0.0001	
Hedges' g	-1.25		-0.70		-0.92	
95% CI	[-1.71, -0.78]		[-1.15, -0.25]		[-1.24, -0.60]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_2_1_m_pth_ckd.sas using SAS 9.4

Table 12.2.1.1.1.s5
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4748		0.5992		0.3726	
Vist 13/ET	0.2266		0.2161		0.0867	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
EAP:n/N1 (%)	24/71 (33.8)	4/36 (11.1)	27/80 (33.8)	3/35 (8.6)	51/151 (33.8)	7/71 (9.9)
RR [95%-CI]; p-value	3.04 [1.14, 8.10], 0.0260		3.94 [1.28, 12.12], 0.0169		3.43 [1.64, 7.17], 0.0011	
OR [95%-CI]; p-value	4.09 [1.29, 12.90], 0.0116		5.43 [1.52, 19.37], 0.0047		4.66 [1.99, 10.91], 0.0002	
RD [95%-CI]; p-value	0.23 [0.08, 0.38], 0.0031		0.25 [0.11, 0.39], 0.0004		0.24 [0.14, 0.34], <0.0001	
Vist 13/ET:n/N1 (%)	26/71 (36.6)	5/36 (13.9)	29/80 (36.3)	5/35 (14.3)	55/151 (36.4)	10/71 (14.1)
RR [95%-CI]; p-value	2.64 [1.11, 6.29], 0.0288		2.54 [1.07, 6.01], 0.0342		2.59 [1.40, 4.77], 0.0023	
OR [95%-CI]; p-value	3.58 [1.24, 10.35], 0.0143		3.41 [1.19, 9.76], 0.0175		3.49 [1.66, 7.37], 0.0006	
RD [95%-CI]; p-value	0.23 [0.07, 0.39], 0.0051		0.22 [0.06, 0.38], 0.0060		0.22 [0.11, 0.33], <0.0001	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
EAP:n/N2 (%)	22/70 (31.4)	2/36 (5.6)	22/64 (34.4)	2/37 (5.4)	44/134 (32.8)	4/73 (5.5)
RR [95%-CI]; p-value	5.66 [1.41, 22.73], 0.0146		6.36 [1.58, 25.53], 0.0091		5.99 [2.24, 16.02], 0.0004	
OR [95%-CI]; p-value	7.79 [1.72, 35.37], 0.0026		9.17 [2.01, 41.72], 0.0010		8.43 [2.89, 24.60], <0.0001	
RD [95%-CI]; p-value	0.26 [0.13, 0.39], 0.0001		0.29 [0.15, 0.43], <0.0001		0.27 [0.18, 0.37], <0.0001	
Vist 13/ET:n/N2 (%)	28/70 (40.0)	2/36 (5.6)	32/64 (50.0)	3/37 (8.1)	60/134 (44.8)	5/73 (6.8)
RR [95%-CI]; p-value	7.20 [1.82, 28.54], 0.0050		6.17 [2.03, 18.75], 0.0013		6.54 [2.75, 15.55], <0.0001	
OR [95%-CI]; p-value	11.33 [2.52, 51.00], 0.0002		11.33 [3.16, 40.68], <0.0001		11.03 [4.18, 29.09], <0.0001	
RD [95%-CI]; p-value	0.34 [0.21, 0.48], <0.0001		0.42 [0.27, 0.57], <0.0001		0.38 [0.28, 0.48], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_1_1_1_m_pth30pct_ckd.sas using SAS 9.4

Table 12.2.1.1.2.s5
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3843		0.3457		0.1995	
Vist 13/ET	0.2673		0.7218		0.3047	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
EAP:n/N1 (%)	43/71 (60.6)	10/36 (27.8)	52/80 (65.0)	11/35 (31.4)	95/151 (62.9)	21/71 (29.6)
RR [95%-CI]; p-value	2.18 [1.25, 3.81], 0.0063		2.07 [1.24, 3.46], 0.0057		2.13 [1.46, 3.11], <0.0001	
OR [95%-CI]; p-value	3.99 [1.67, 9.54], 0.0014		4.05 [1.73, 9.47], 0.0009		4.04 [2.20, 7.41], <0.0001	
RD [95%-CI]; p-value	0.33 [0.14, 0.51], 0.0005		0.34 [0.15, 0.52], 0.0004		0.33 [0.20, 0.46], <0.0001	
Vist 13/ET:n/N1 (%)	42/71 (59.2)	11/36 (30.6)	56/80 (70.0)	11/35 (31.4)	98/151 (64.9)	22/71 (31.0)
RR [95%-CI]; p-value	1.94 [1.14, 3.29], 0.0144		2.23 [1.34, 3.71], 0.0021		2.09 [1.45, 3.02], <0.0001	
OR [95%-CI]; p-value	3.29 [1.40, 7.72], 0.0052		5.09 [2.16, 12.02], 0.0001		4.12 [2.25, 7.53], <0.0001	
RD [95%-CI]; p-value	0.29 [0.10, 0.47], 0.0030		0.39 [0.20, 0.57], <0.0001		0.34 [0.21, 0.47], <0.0001	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
EAP:n/N2 (%)	44/70 (62.9)	7/36 (19.4)	38/64 (59.4)	7/37 (18.9)	82/134 (61.2)	14/73 (19.2)
RR [95%-CI]; p-value	3.23 [1.62, 6.44], 0.0008		3.14 [1.56, 6.30], 0.0013		3.19 [1.96, 5.21], <0.0001	
OR [95%-CI]; p-value	7.01 [2.69, 18.26], <0.0001		6.26 [2.39, 16.39], <0.0001		6.65 [3.37, 13.10], <0.0001	
RD [95%-CI]; p-value	0.43 [0.26, 0.61], <0.0001		0.40 [0.23, 0.58], <0.0001		0.42 [0.30, 0.54], <0.0001	
Vist 13/ET:n/N2 (%)	48/70 (68.6)	8/36 (22.2)	40/64 (62.5)	9/37 (24.3)	88/134 (65.7)	17/73 (23.3)
RR [95%-CI]; p-value	3.09 [1.64, 5.80], 0.0005		2.57 [1.41, 4.68], 0.0020		2.82 [1.83, 4.35], <0.0001	
OR [95%-CI]; p-value	7.64 [3.00, 19.43], <0.0001		5.19 [2.10, 12.83], 0.0002		6.30 [3.29, 12.06], <0.0001	
RD [95%-CI]; p-value	0.46 [0.29, 0.64], <0.0001		0.38 [0.20, 0.56], <0.0001		0.42 [0.30, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_2_1_1_2_m_pth10pct_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7851		0.9940		0.8801	
Comparison Baseline vs. EAP	0.3711		0.4996		0.2700	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	20.8 (5.02)	19.5 (5.82)	19.9 (5.64)	18.8 (5.43)	20.3 (5.36)	19.2 (5.60)
Visit 13/ET						
n/N1	64/71	35/36	72/80	29/35	136/151	64/71
Mean (SD)	65.6 (25.91)	18.3 (6.59)	63.6 (22.57)	19.9 (6.44)	64.5 (24.13)	19.0 (6.52)
EAP						
n/N1	58/71	33/36	69/80	30/35	127/151	63/71
Mean (SD)	67.6 (23.96)	18.5 (6.73)	64.9 (21.10)	19.2 (6.04)	66.1 (22.40)	18.8 (6.37)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.8 (2.52)	-1.1 (3.42)	43.6 (2.24)	0.1 (3.53)	44.2 (1.68)	-0.6 (2.46)
95% CI	[39.77, 49.80]	[-7.85, 5.72]	[39.16, 48.06]	[-6.95, 7.08]	[40.92, 47.57]	[-5.44, 4.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.85		43.54		44.82	
95% CI	[37.40, 54.30]		[35.23, 51.85]		[38.93, 50.71]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.28		2.28		2.30	
95% CI	[1.76, 2.79]		[1.74, 2.81]		[1.92, 2.67]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (2.46)	-0.7 (3.27)	45.0 (2.09)	-0.1 (3.17)	46.0 (1.60)	-0.4 (2.27)
95% CI	[42.07, 51.86]	[-7.22, 5.78]	[40.87, 49.16]	[-6.35, 6.23]	[42.84, 49.17]	[-4.89, 4.07]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.69		45.07		46.42	
95% CI	[39.53, 55.85]		[37.53, 52.61]		[40.92, 51.91]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.55		2.59		2.59	
95% CI	[1.98, 3.11]		[2.03, 3.14]		[2.19, 2.98]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	19.7 (5.11)	18.9 (5.09)	19.4 (5.49)	19.9 (5.61)	19.5 (5.28)	19.4 (5.35)
Visit 13/ET						
n/N2	67/70	33/36	60/64	33/37	127/134	66/73
Mean (SD)	64.6 (23.50)	16.7 (5.69)	68.2 (26.75)	19.8 (7.05)	66.3 (25.05)	18.3 (6.56)
EAP						
n/N2	60/70	31/36	55/64	31/37	115/134	62/73
Mean (SD)	66.5 (20.66)	16.7 (5.67)	69.1 (21.77)	19.7 (7.02)	67.7 (21.14)	18.2 (6.50)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.2.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.2 (2.39)	-2.5 (3.41)	49.0 (2.77)	0.0 (3.74)	47.1 (1.82)	-1.1 (2.52)
95% CI	[40.50, 50.00]	[-9.24, 4.29]	[43.48, 54.48]	[-7.39, 7.45]	[43.47, 50.65]	[-6.09, 3.86]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.73		48.95		48.17	
95% CI	[39.45, 56.00]		[39.71, 58.20]		[42.03, 54.31]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.38		2.28		2.34	
95% CI	[1.85, 2.91]		[1.74, 2.81]		[1.96, 2.71]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.4 (2.18)	-2.5 (3.04)	49.8 (2.32)	0.2 (3.09)	48.6 (1.59)	-1.1 (2.16)
95% CI	[43.01, 51.69]	[-8.50, 3.57]	[45.15, 54.37]	[-5.93, 6.36]	[45.42, 51.69]	[-5.39, 3.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.81		49.55		49.67	
95% CI	[42.39, 57.24]		[41.86, 57.23]		[44.38, 54.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.92		2.87		2.92	
95% CI	[2.32, 3.53]		[2.26, 3.48]		[2.48, 3.35]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_2_1_m_25d_ckd.sas using SAS 9.4

Table 12.3.1.1.s5
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.3487		0.2206		0.7533	
Vist 13/ET	0.9431		0.4776		0.5618	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
EAP:n/N1 (%)	55/71 (77.5)	2/36 (5.6)	67/80 (83.8)	1/35 (2.9)	122/151 (80.8)	3/71 (4.2)
RR [95%-CI]; p-value	13.94 [3.61, 53.93], 0.0001		29.31 [4.24, 202.79], 0.0006		19.12 [6.30, 58.03], <0.0001	
OR [95%-CI]; p-value	58.44 [12.64, 270.12], <0.0001		175.23 [21.99, 1396.19], <0.0001		95.36 [28.01, 324.65], <0.0001	
RD [95%-CI]; p-value	0.72 [0.60, 0.84], <0.0001		0.81 [0.71, 0.91], <0.0001		0.77 [0.69, 0.84], <0.0001	
Vist 13/ET:n/N1 (%)	56/71 (78.9)	1/36 (2.8)	67/80 (83.8)	2/35 (5.7)	123/151 (81.5)	3/71 (4.2)
RR [95%-CI]; p-value	28.39 [4.10, 196.86], 0.0007		14.66 [3.80, 56.49], <0.0001		19.28 [6.35, 58.50], <0.0001	
OR [95%-CI]; p-value	130.67 [16.52, 1033.26], <0.0001		85.04 [18.12, 399.04], <0.0001		99.57 [29.19, 339.62], <0.0001	
RD [95%-CI]; p-value	0.76 [0.65, 0.87], <0.0001		0.78 [0.67, 0.89], <0.0001		0.77 [0.69, 0.85], <0.0001	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
EAP:n/N2 (%)	58/70 (82.9)	0/36 (0.0)	53/64 (82.8)	4/37 (10.8)	111/134 (82.8)	4/73 (5.5)
RR [95%-CI]; p-value	60.49 [3.85, 950.73], 0.0035		7.66 [3.02, 19.46], <0.0001		15.12 [5.81, 39.32], <0.0001	
OR [95%-CI]; p-value	348.00 [19.94, 6072.76], <0.0001		39.75 [11.69, 135.20], <0.0001		83.25 [27.62, 250.97], <0.0001	
RD [95%-CI]; p-value	0.81 [0.72, 0.91], <0.0001		0.72 [0.58, 0.86], <0.0001		0.77 [0.69, 0.86], <0.0001	
Vist 13/ET:n/N2 (%)	61/70 (87.1)	1/36 (2.8)	56/64 (87.5)	4/37 (10.8)	117/134 (87.3)	5/73 (6.8)
RR [95%-CI]; p-value	31.37 [4.53, 217.14], 0.0005		8.09 [3.19, 20.52], <0.0001		12.75 [5.46, 29.78], <0.0001	
OR [95%-CI]; p-value	237.22 [28.84, 1951.53], <0.0001		57.75 [16.14, 206.66], <0.0001		93.60 [33.05, 265.07], <0.0001	
RD [95%-CI]; p-value	0.84 [0.75, 0.94], <0.0001		0.77 [0.64, 0.90], <0.0001		0.80 [0.72, 0.89], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_3_1_1_m_25d30_ckd.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4445		0.7408		0.9618	
Comparison Baseline vs. EAP	0.0520		0.7196		0.3442	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	97.9 (9.56)	100.3 (9.79)	99.6 (9.03)	102.7 (7.22)	98.9 (9.26)	101.3 (8.76)
Visit 13/ET						
n/N1	39/43	25/26	50/53	18/20	89/96	43/46
Mean (SD)	84.6 (40.23)	111.0 (41.97)	77.4 (29.69)	111.3 (41.71)	80.6 (34.68)	111.1 (41.36)
EAP						
n/N1	36/43	24/26	49/53	17/20	85/96	41/46
Mean (SD)	84.4 (35.82)	103.4 (34.83)	79.7 (29.73)	108.7 (25.78)	81.7 (32.33)	105.6 (31.15)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-13.1 (6.48)	10.4 (8.12)	-22.2 (4.59)	8.6 (7.69)	-17.6 (3.89)	9.5 (5.65)
95% CI	[-26.08, -0.15]	[-5.81, 26.66]	[-31.32, -13.01]	[-6.78, 23.94]	[-25.33, -9.94]	[-1.67, 20.69]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-23.54		-30.74		-27.15	
95% CI	[-44.44, -2.64]		[-48.72, -12.77]		[-40.80, -13.50]	
p-value	0.0279		0.0011		0.0001	
Hedges' g	-0.58		-0.95		-0.76	
95% CI	[-1.08, -0.07]		[-1.50, -0.39]		[-1.14, -0.39]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-13.2 (5.59)	2.7 (6.86)	-19.8 (3.80)	4.9 (6.49)	-16.5 (3.29)	3.8 (4.77)
95% CI	[-24.43, -2.04]	[-11.01, 16.45]	[-27.43, -12.24]	[-8.10, 17.85]	[-23.03, -10.00]	[-5.62, 13.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-15.96		-24.71		-20.34	
95% CI	[-33.74, 1.82]		[-39.81, -9.60]		[-31.86, -8.82]	
p-value	0.0776		0.0018		0.0007	
Hedges' g	-0.49		-0.96		-0.72	
95% CI	[-1.01, 0.02]		[-1.53, -0.39]		[-1.10, -0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	133.1 (10.45)	133.1 (12.01)	132.5 (12.32)	135.0 (11.41)	132.8 (11.31)	134.2 (11.59)
Visit 13/ET						
n/N2	46/50	22/22	42/44	23/28	88/94	45/50
Mean (SD)	102.6 (32.28)	133.5 (39.56)	111.7 (39.57)	146.2 (57.90)	107.0 (36.03)	140.0 (49.64)
EAP						
n/N2	43/50	22/22	40/44	23/28	83/94	45/50
Mean (SD)	97.8 (27.58)	137.1 (33.13)	110.5 (34.02)	142.5 (39.65)	103.9 (31.32)	139.9 (36.29)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.6 (5.12)	0.3 (7.41)	-20.5 (6.86)	11.3 (9.28)	-25.8 (4.36)	6.4 (6.09)
95% CI	[-40.78, -20.32]	[-14.49, 15.11]	[-34.22, -6.78]	[-7.23, 29.88]	[-34.44, -17.21]	[-5.68, 18.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-30.86		-31.83		-32.19	
95% CI	[-48.85, -12.87]		[-54.94, -8.72]		[-47.01, -17.38]	
p-value	0.0011		0.0077		<0.0001	
Hedges' g	-0.81		-0.72		-0.78	
95% CI	[-1.34, -0.29]		[-1.24, -0.21]		[-1.15, -0.41]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-35.9 (4.47)	3.8 (6.25)	-22.2 (5.33)	9.0 (7.03)	-29.1 (3.48)	6.5 (4.72)
95% CI	[-44.86, -26.98]	[-8.74, 16.26]	[-32.83, -11.51]	[-5.10, 23.02]	[-36.02, -22.25]	[-2.82, 15.87]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-39.68		-31.13		-35.66	
95% CI	[-55.05, -24.31]		[-48.78, -13.49]		[-47.26, -24.05]	
p-value	<0.0001		0.0008		<0.0001	
Hedges' g	-1.33		-0.92		-1.12	
95% CI	[-1.89, -0.78]		[-1.45, -0.39]		[-1.51, -0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	205.0 (57.47)	195.9 (35.37)	215.8 (70.38)	223.6 (65.71)	210.4 (64.07)	209.8 (54.04)
Visit 13/ET						
n/N3	44/48	21/24	40/47	22/24	84/95	43/48
Mean (SD)	152.5 (80.19)	209.4 (68.08)	169.3 (141.35)	242.6 (80.42)	160.5 (113.10)	226.4 (75.65)
EAP						
n/N3	38/48	18/24	35/47	21/24	73/95	39/48
Mean (SD)	146.7 (62.24)	214.0 (72.02)	162.8 (119.69)	212.1 (70.37)	154.4 (93.92)	213.0 (70.20)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s6
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-53.2 (9.94)	14.6 (14.43)	-43.0 (13.80)	11.5 (18.64)	-49.4 (8.55)	15.6 (11.94)
95% CI	[-73.03, -33.27]		[-70.60, -15.38]		[-66.30, -32.46]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-67.75		-54.52		-65.01	
95% CI	[-102.92, -32.59]		[-101.04, -8.01]		[-94.07, -35.94]	
p-value	0.0003		0.0224		<0.0001	
Hedges' g	-1.06		-0.65		-0.84	
95% CI	[-1.60, -0.51]		[-1.18, -0.13]		[-1.22, -0.46]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-53.4 (9.12)	19.0 (13.27)	-50.0 (11.76)	-3.4 (15.19)	-52.0 (7.47)	8.5 (10.25)
95% CI	[-71.74, -35.14]		[-73.56, -26.37]		[-66.86, -37.23]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-72.46		-46.57		-60.57	
95% CI	[-104.79, -40.13]		[-85.11, -8.04]		[-85.71, -35.42]	
p-value	<0.0001		0.0188		<0.0001	
Hedges' g	-1.29		-0.66		-0.94	
95% CI	[-1.89, -0.69]		[-1.21, -0.12]		[-1.34, -0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_2_1_m_pth_ttlpth.sas using SAS 9.4

Table 12.2.1.1.1.s6
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.5024		0.8412		0.8755	
Vist 13/ET	0.4599		0.6414		0.3316	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
EAP:n/N1 (%)	11/43 (25.6)	3/26 (11.5)	19/53 (35.8)	1/20 (5.0)	30/96 (31.3)	4/46 (8.7)
RR [95%-CI]; p-value	2.22 [0.68, 7.22], 0.1861		7.17 [1.03, 50.09], 0.0470		3.59 [1.35, 9.60], 0.0107	
OR [95%-CI]; p-value	2.64 [0.66, 10.52], 0.1598		10.62 [1.32, 85.65], 0.0084		4.77 [1.57, 14.52], 0.0032	
RD [95%-CI]; p-value	0.14 [-0.04, 0.32], 0.1244		0.31 [0.15, 0.47], 0.0002		0.23 [0.10, 0.35], 0.0003	
Vist 13/ET:n/N1 (%)	13/43 (30.2)	3/26 (11.5)	24/53 (45.3)	3/20 (15.0)	37/96 (38.5)	6/46 (13.0)
RR [95%-CI]; p-value	2.62 [0.82, 8.33], 0.1028		3.02 [1.02, 8.93], 0.0458		2.95 [1.34, 6.50], 0.0070	
OR [95%-CI]; p-value	3.32 [0.85, 13.05], 0.0746		4.69 [1.23, 17.93], 0.0168		4.18 [1.61, 10.83], 0.0020	
RD [95%-CI]; p-value	0.19 [0.00, 0.37], 0.0467		0.30 [0.10, 0.51], 0.0040		0.25 [0.12, 0.39], 0.0003	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
EAP:n/N2 (%)	19/50 (38.0)	1/22 (4.5)	11/44 (25.0)	2/28 (7.1)	30/94 (31.9)	3/50 (6.0)
RR [95%-CI]; p-value	8.36 [1.19, 58.60], 0.0326		3.50 [0.84, 14.63], 0.0860		5.32 [1.71, 16.57], 0.0039	
OR [95%-CI]; p-value	12.87 [1.60, 103.62], 0.0035		4.33 [0.88, 21.29], 0.0548		7.34 [2.11, 25.51], 0.0004	
RD [95%-CI]; p-value	0.33 [0.17, 0.49], <0.0001		0.18 [0.02, 0.34], 0.0283		0.26 [0.14, 0.37], <0.0001	
Vist 13/ET:n/N2 (%)	20/50 (40.0)	3/22 (13.6)	13/44 (29.5)	3/28 (10.7)	33/94 (35.1)	6/50 (12.0)
RR [95%-CI]; p-value	2.93 [0.97, 8.86], 0.0563		2.76 [0.86, 8.82], 0.0872		2.93 [1.32, 6.51], 0.0085	
OR [95%-CI]; p-value	4.22 [1.10, 16.17], 0.0271		3.49 [0.90, 13.64], 0.0610		3.97 [1.53, 10.28], 0.0030	
RD [95%-CI]; p-value	0.26 [0.07, 0.46], 0.0089		0.19 [0.01, 0.37], 0.0370		0.23 [0.10, 0.36], 0.0006	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_1_m_pth30pct_ttlpth.sas using SAS 9.4

Table 12.2.1.1.1.s6
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
EAP:n/N3 (%)	16/48 (33.3)	2/24 (8.3)	19/47 (40.4)	2/24 (8.3)	35/95 (36.8)	4/48 (8.3)
RR [95%-CI]; p-value	4.00 [1.00, 15.99], 0.0499		4.85 [1.23, 19.12], 0.0240		4.42 [1.67, 11.72], 0.0028	
OR [95%-CI]; p-value	5.50 [1.15, 26.36], 0.0209		7.46 [1.57, 35.53], 0.0051		6.42 [2.12, 19.38], 0.0003	
RD [95%-CI]; p-value	0.25 [0.08, 0.42], 0.0047		0.32 [0.14, 0.50], 0.0004		0.29 [0.16, 0.41], <0.0001	
Vist 13/ET:n/N3 (%)	21/48 (43.8)	1/24 (4.2)	24/47 (51.1)	2/24 (8.3)	45/95 (47.4)	3/48 (6.3)
RR [95%-CI]; p-value	10.50 [1.50, 73.46], 0.0178		6.13 [1.58, 23.78], 0.0088		7.58 [2.48, 23.13], 0.0004	
OR [95%-CI]; p-value	17.89 [2.23, 143.44], 0.0006		11.48 [2.42, 54.43], 0.0004		13.50 [3.92, 46.47], <0.0001	
RD [95%-CI]; p-value	0.40 [0.23, 0.56], <0.0001		0.43 [0.25, 0.61], <0.0001		0.41 [0.29, 0.53], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_1_m_pth30pct_ttlpth.sas using SAS 9.4

Table 12.2.1.1.2.s6
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.4174		0.7153		0.6286	
Vist 13/ET	0.4930		0.6427		0.4158	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
EAP:n/N1 (%)	25/43 (58.1)	8/26 (30.8)	37/53 (69.8)	6/20 (30.0)	62/96 (64.6)	14/46 (30.4)
RR [95%-CI]; p-value	1.89 [1.01, 3.55], 0.0477		2.33 [1.16, 4.65], 0.0168		2.12 [1.34, 3.37], 0.0014	
OR [95%-CI]; p-value	3.13 [1.12, 8.75], 0.0274		5.40 [1.76, 16.57], 0.0020		4.17 [1.96, 8.86], 0.0001	
RD [95%-CI]; p-value	0.27 [0.04, 0.50], 0.0200		0.40 [0.16, 0.63], 0.0009		0.34 [0.18, 0.51], <0.0001	
Vist 13/ET:n/N1 (%)	27/43 (62.8)	7/26 (26.9)	36/53 (67.9)	7/20 (35.0)	63/96 (65.6)	14/46 (30.4)
RR [95%-CI]; p-value	2.33 [1.19, 4.57], 0.0138		1.94 [1.04, 3.63], 0.0377		2.16 [1.36, 3.42], 0.0011	
OR [95%-CI]; p-value	4.58 [1.58, 13.28], 0.0039		3.93 [1.33, 11.64], 0.0108		4.36 [2.05, 9.30], <0.0001	
RD [95%-CI]; p-value	0.36 [0.14, 0.58], 0.0017		0.33 [0.09, 0.57], 0.0082		0.35 [0.19, 0.52], <0.0001	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
EAP:n/N2 (%)	36/50 (72.0)	6/22 (27.3)	25/44 (56.8)	5/28 (17.9)	61/94 (64.9)	11/50 (22.0)
RR [95%-CI]; p-value	2.64 [1.31, 5.34], 0.0069		3.18 [1.38, 7.33], 0.0066		2.95 [1.71, 5.08], <0.0001	
OR [95%-CI]; p-value	6.86 [2.23, 21.08], 0.0004		6.05 [1.94, 18.86], 0.0011		6.55 [2.97, 14.47], <0.0001	
RD [95%-CI]; p-value	0.45 [0.22, 0.67], <0.0001		0.39 [0.19, 0.59], 0.0002		0.43 [0.28, 0.58], <0.0001	
Vist 13/ET:n/N2 (%)	34/50 (68.0)	8/22 (36.4)	29/44 (65.9)	8/28 (28.6)	63/94 (67.0)	16/50 (32.0)
RR [95%-CI]; p-value	1.87 [1.04, 3.36], 0.0358		2.31 [1.24, 4.30], 0.0085		2.09 [1.36, 3.21], 0.0007	
OR [95%-CI]; p-value	3.72 [1.30, 10.65], 0.0121		4.83 [1.73, 13.54], 0.0020		4.32 [2.07, 8.99], <0.0001	
RD [95%-CI]; p-value	0.32 [0.08, 0.56], 0.0095		0.37 [0.16, 0.59], 0.0008		0.35 [0.19, 0.51], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_2_m_pth10pct_ttlpth.sas using SAS 9.4

Table 12.2.1.1.2.s6
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
EAP:n/N3 (%)	26/48 (54.2)	3/24 (12.5)	28/47 (59.6)	7/24 (29.2)	54/95 (56.8)	10/48 (20.8)
RR [95%-CI]; p-value	4.33 [1.46, 12.89], 0.0084		2.04 [1.05, 3.98], 0.0357		2.73 [1.53, 4.87], 0.0007	
OR [95%-CI]; p-value	8.27 [2.17, 31.48], 0.0007		3.58 [1.25, 10.28], 0.0153		5.00 [2.23, 11.21], <0.0001	
RD [95%-CI]; p-value	0.42 [0.22, 0.61], <0.0001		0.30 [0.07, 0.53], 0.0095		0.36 [0.21, 0.51], <0.0001	
Vist 13/ET:n/N3 (%)	29/48 (60.4)	4/24 (16.7)	31/47 (66.0)	5/24 (20.8)	60/95 (63.2)	9/48 (18.8)
RR [95%-CI]; p-value	3.63 [1.44, 9.13], 0.0063		3.17 [1.41, 7.09], 0.0051		3.37 [1.83, 6.19], <0.0001	
OR [95%-CI]; p-value	7.63 [2.25, 25.84], 0.0004		7.36 [2.32, 23.37], 0.0003		7.43 [3.22, 17.14], <0.0001	
RD [95%-CI]; p-value	0.44 [0.23, 0.64], <0.0001		0.45 [0.24, 0.66], <0.0001		0.44 [0.30, 0.59], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_2_1_1_2_m_pth10pct_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4366		0.6279		0.2655	
Comparison Baseline vs. EAP	0.9219		0.9898		0.9316	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	20.8 (5.29)	20.8 (5.88)	20.6 (5.26)	21.2 (5.13)	20.6 (5.25)	21.0 (5.51)
Visit 13/ET						
n/N1	40/43	25/26	50/53	18/20	90/96	43/46
Mean (SD)	67.1 (26.33)	18.1 (6.80)	69.1 (22.52)	20.4 (5.37)	68.2 (24.16)	19.1 (6.28)
EAP						
n/N1	36/43	24/26	49/53	17/20	85/96	41/46
Mean (SD)	66.7 (23.64)	18.3 (6.61)	69.8 (20.67)	20.8 (6.31)	68.5 (21.89)	19.3 (6.52)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.6 (3.21)	-2.9 (4.06)	48.1 (2.78)	-0.9 (4.63)	47.3 (2.12)	-2.0 (3.09)
95% CI	[40.13, 52.97]	[-11.00, 5.24]	[42.56, 53.65]	[-10.20, 8.32]	[43.15, 51.54]	[-8.11, 4.12]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.43		49.05		49.34	
95% CI	[39.08, 59.78]		[38.25, 59.85]		[41.92, 56.76]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.42		2.49		2.50	
95% CI	[1.77, 3.07]		[1.81, 3.16]		[2.03, 2.97]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.4 (3.01)	-2.5 (3.68)	49.2 (2.54)	-0.8 (4.33)	47.8 (1.96)	-1.7 (2.83)
95% CI	[40.41, 52.46]	[-9.87, 4.89]	[44.09, 54.26]	[-9.41, 7.88]	[43.93, 51.69]	[-7.26, 3.95]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.92		49.94		49.46	
95% CI	[39.40, 58.45]		[39.89, 59.98]		[42.64, 56.29]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.70		2.80		2.80	
95% CI	[2.00, 3.40]		[2.08, 3.53]		[2.30, 3.31]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	19.8 (4.45)	17.7 (5.49)	20.5 (5.85)	19.1 (5.31)	20.2 (5.14)	18.5 (5.38)
Visit 13/ET						
n/N2	47/50	22/22	42/44	23/28	89/94	45/50
Mean (SD)	66.8 (21.74)	16.2 (5.76)	60.2 (19.67)	20.5 (6.81)	63.7 (20.94)	18.4 (6.61)
EAP						
n/N2	44/50	22/22	40/44	23/28	84/94	45/50
Mean (SD)	69.0 (20.79)	16.6 (6.28)	60.2 (18.55)	19.4 (5.77)	64.8 (20.13)	18.1 (6.12)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	47.5 (2.71)	-2.6 (3.99)	40.1 (2.51)	0.6 (3.39)	43.8 (1.85)	-0.9 (2.60)
95% CI	[42.10, 52.91]	[-10.59, 5.34]	[35.08, 45.10]	[-6.13, 7.42]	[40.10, 47.41]	[-6.02, 4.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.13		39.45		44.63	
95% CI	[40.41, 59.85]		[31.02, 47.87]		[38.30, 50.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.56		2.37		2.47	
95% CI	[1.90, 3.22]		[1.72, 3.02]		[2.01, 2.93]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	49.8 (2.66)	-2.1 (3.79)	40.1 (2.30)	0.1 (3.03)	44.9 (1.77)	-0.8 (2.42)
95% CI	[44.46, 55.08]	[-9.64, 5.49]	[35.53, 44.71]	[-5.94, 6.19]	[41.37, 48.37]	[-5.59, 3.99]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.84		39.99		45.67	
95% CI	[42.52, 61.17]		[32.38, 47.61]		[39.71, 51.63]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.79		2.74		2.72	
95% CI	[2.10, 3.49]		[2.04, 3.43]		[2.23, 3.21]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	20.1 (5.55)	19.0 (4.56)	17.8 (5.26)	18.1 (5.86)	19.0 (5.50)	18.6 (5.21)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	61.5 (26.02)	18.1 (5.91)	67.2 (30.58)	18.7 (7.75)	64.2 (28.26)	18.4 (6.81)
EAP						
n/N3	38/48	18/24	35/47	21/24	73/95	39/48
Mean (SD)	65.1 (22.95)	18.0 (5.92)	70.0 (24.22)	18.4 (7.48)	67.4 (23.53)	18.2 (6.72)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.2.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	41.6 (3.19)	-0.7 (4.62)	49.9 (3.73)	-0.0 (5.15)	45.6 (2.44)	-0.1 (3.44)
95% CI	[35.18, 47.92]		[42.42, 57.34]		[40.80, 50.45]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.23		49.91		45.77	
95% CI	[30.99, 53.47]		[37.17, 62.66]		[37.42, 54.12]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.00		2.05		2.02	
95% CI	[1.38, 2.61]		[1.41, 2.69]		[1.58, 2.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	45.5 (2.90)	-1.1 (4.21)	52.1 (3.13)	0.9 (4.04)	48.8 (2.12)	-0.1 (2.91)
95% CI	[39.69, 51.31]		[45.86, 58.42]		[44.61, 53.03]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.62		51.26		48.94	
95% CI	[36.36, 56.88]		[41.01, 61.52]		[41.80, 56.08]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.58		2.74		2.67	
95% CI	[1.85, 3.32]		[2.01, 3.48]		[2.15, 3.19]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_2_1_m_25d_ttlpth.sas using SAS 9.4

Table 12.3.1.1.s6
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.9306		0.3432		0.4963	
Vist 13/ET	0.8627		0.4837		0.3812	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
EAP:n/N1 (%)	35/43 (81.4)	1/26 (3.8)	49/53 (92.5)	2/20 (10.0)	84/96 (87.5)	3/46 (6.5)
RR [95%-CI]; p-value	21.16 [3.08, 145.39], 0.0019		9.25 [2.48, 34.51], 0.0009		13.42 [4.48, 40.17], <0.0001	
OR [95%-CI]; p-value	109.38 [12.85, 930.81], <0.0001		110.25 [18.57, 654.59], <0.0001		100.33 [26.87, 374.63], <0.0001	
RD [95%-CI]; p-value	0.78 [0.64, 0.91], <0.0001		0.82 [0.68, 0.97], <0.0001		0.81 [0.71, 0.91], <0.0001	
Vist 13/ET:n/N1 (%)	36/43 (83.7)	0/26 (0.0)	49/53 (92.5)	1/20 (5.0)	85/96 (88.5)	1/46 (2.2)
RR [95%-CI]; p-value	44.37 [2.84, 693.19], 0.0068		18.49 [2.73, 125.10], 0.0028		40.73 [5.85, 283.39], 0.0002	
OR [95%-CI]; p-value	267.43 [14.52, 4924.38], <0.0001		232.75 [24.42, 2218.05], <0.0001		347.73 [43.50, 2779.92], <0.0001	
RD [95%-CI]; p-value	0.82 [0.70, 0.94], <0.0001		0.87 [0.76, 0.99], <0.0001		0.86 [0.79, 0.94], <0.0001	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
EAP:n/N2 (%)	43/50 (86.0)	1/22 (4.5)	38/44 (86.4)	0/28 (0.0)	81/94 (86.2)	1/50 (2.0)
RR [95%-CI]; p-value	18.92 [2.78, 128.82], 0.0027		49.23 [3.15, 769.96], 0.0055		43.09 [6.18, 300.41], 0.0001	
OR [95%-CI]; p-value	129.00 [14.89, 1117.77], <0.0001		354.67 [19.01, 6615.52], <0.0001		305.31 [38.73, 2406.60], <0.0001	
RD [95%-CI]; p-value	0.81 [0.68, 0.94], <0.0001		0.85 [0.73, 0.96], <0.0001		0.84 [0.76, 0.92], <0.0001	
Vist 13/ET:n/N2 (%)	43/50 (86.0)	1/22 (4.5)	40/44 (90.9)	2/28 (7.1)	83/94 (88.3)	3/50 (6.0)
RR [95%-CI]; p-value	18.92 [2.78, 128.82], 0.0027		12.73 [3.34, 48.55], 0.0002		14.72 [4.90, 44.19], <0.0001	
OR [95%-CI]; p-value	129.00 [14.89, 1117.77], <0.0001		130.00 [22.19, 761.48], <0.0001		118.21 [31.40, 445.09], <0.0001	
RD [95%-CI]; p-value	0.81 [0.68, 0.94], <0.0001		0.84 [0.71, 0.97], <0.0001		0.82 [0.73, 0.92], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_1_1_m_25d30_ttlpth.sas using SAS 9.4

Table 12.3.1.1.s6
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
EAP:n/N3 (%)	35/48 (72.9)	0/24 (0.0)	33/47 (70.2)	3/24 (12.5)	68/95 (71.6)	3/48 (6.3)
RR [95%-CI]; p-value	35.73 [2.29, 558.22], 0.0108		5.62 [1.92, 16.45], 0.0016		11.45 [3.80, 34.51], <0.0001	
OR [95%-CI]; p-value	129.23 [7.31, 2283.75], <0.0001		16.50 [4.23, 64.40], <0.0001		37.78 [10.81, 131.97], <0.0001	
RD [95%-CI]; p-value	0.71 [0.57, 0.85], <0.0001		0.58 [0.39, 0.76], <0.0001		0.65 [0.54, 0.77], <0.0001	
Vist 13/ET:n/N3 (%)	38/48 (79.2)	1/24 (4.2)	34/47 (72.3)	3/24 (12.5)	72/95 (75.8)	4/48 (8.3)
RR [95%-CI]; p-value	19.00 [2.77, 130.14], 0.0027		5.79 [1.98, 16.93], 0.0013		9.09 [3.53, 23.40], <0.0001	
OR [95%-CI]; p-value	87.40 [10.49, 728.02], <0.0001		18.31 [4.66, 71.92], <0.0001		34.43 [11.17, 106.18], <0.0001	
RD [95%-CI]; p-value	0.75 [0.61, 0.89], <0.0001		0.60 [0.41, 0.78], <0.0001		0.67 [0.56, 0.79], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_3_1_1_m_25d30_ttlpth.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4687		0.7147		0.8175	
Comparison Baseline vs. EAP	0.2586		0.3813		0.2129	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	142.4 (71.43)	99.7 (11.50)	122.2 (55.07)	116.4 (30.00)	129.4 (61.52)	108.1 (23.15)
Visit 13/ET						
n/N1	17/18	5/5	30/32	4/5	47/50	9/10
Mean (SD)	120.9 (74.37)	106.4 (45.36)	86.9 (38.25)	105.8 (35.28)	99.2 (55.85)	106.1 (38.67)
EAP						
n/N1	14/18	5/5	30/32	4/5	44/50	9/10
Mean (SD)	128.1 (65.16)	96.5 (41.58)	89.3 (38.10)	104.9 (20.58)	101.6 (50.96)	100.2 (32.30)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-20.9 (14.46)	-7.4 (27.36)	-26.9 (6.06)	1.0 (16.74)	-23.1 (6.85)	-2.6 (15.18)
95% CI	[-51.13, 9.42]	[-64.66, 49.88]	[-39.30, -14.59]	[-33.16, 35.12]	[-36.88, -9.38]	[-33.05, 27.92]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-13.46		-27.93		-20.57	
95% CI	[-79.29, 52.36]		[-64.32, 8.46]		[-54.41, 13.27]	
p-value	0.6734		0.1277		0.2279	
Hedges' g	-0.48		-0.88		-0.67	
95% CI	[-1.45, 0.49]		[-1.92, 0.16]		[-1.38, 0.04]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-21.9 (12.09)	-18.1 (20.92)	-25.0 (6.13)	-13.9 (16.83)	-22.2 (6.15)	-14.6 (12.58)
95% CI	[-47.58, 3.68]	[-62.44, 26.24]	[-37.53, -12.55]	[-48.19, 20.46]	[-34.56, -9.83]	[-39.89, 10.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-3.84		-11.17		-7.60	
95% CI	[-56.42, 48.73]		[-47.73, 25.38]		[-36.06, 20.86]	
p-value	0.8787		0.5376		0.5938	
Hedges' g	-0.47		-0.25		-0.42	
95% CI	[-1.45, 0.52]		[-1.27, 0.77]		[-1.13, 0.29]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	143.6 (47.03)	144.7 (45.21)	152.4 (66.36)	155.1 (57.67)	147.8 (57.08)	149.8 (51.76)
Visit 13/ET						
n/N2	105/108	62/63	94/98	57/61	199/206	119/124
Mean (SD)	111.0 (58.03)	153.2 (65.59)	120.3 (98.75)	167.4 (76.02)	115.4 (79.82)	160.0 (70.83)
EAP						
n/N2	103/108	59/63	94/98	57/61	197/206	116/124
Mean (SD)	107.0 (48.56)	150.3 (65.28)	120.7 (83.69)	160.7 (65.43)	113.6 (67.80)	155.4 (65.28)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.2.1.s7
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.7 (4.65)	10.1 (6.05)	-32.1 (6.63)	11.5 (8.51)	-31.9 (3.99)	10.9 (5.16)
95% CI	[-40.91, -22.54]	[-1.85, 22.05]	[-45.21, -19.02]	[-5.29, 28.35]	[-39.79, -24.08]	[0.72, 21.03]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-41.83		-43.64		-42.81	
95% CI	[-56.90, -26.75]		[-64.97, -22.32]		[-55.66, -29.97]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.86		-0.68		-0.76	
95% CI	[-1.19, -0.54]		[-1.01, -0.34]		[-0.99, -0.52]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-35.9 (4.08)	9.0 (5.38)	-30.8 (5.05)	5.4 (6.49)	-33.4 (3.23)	7.3 (4.20)
95% CI	[-43.90, -27.81]	[-1.66, 19.61]	[-40.76, -20.79]	[-7.39, 18.26]	[-39.71, -27.01]	[-0.93, 15.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.83		-36.21		-40.70	
95% CI	[-58.17, -31.49]		[-52.46, -19.96]		[-51.12, -30.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.07		-0.73		-0.89	
95% CI	[-1.41, -0.73]		[-1.07, -0.39]		[-1.13, -0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_2_1_m_pth_dose.sas using SAS 9.4

Table 12.2.1.1.1.s7

Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH

ITT Population

Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0641		0.2408		0.0560	
Vist 13/ET	0.4420		0.5878		0.3751	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
EAP:n/N1 (%)	2/18 (11.1)	1/5 (20.0)	11/32 (34.4)	1/5 (20.0)	13/50 (26.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		1.72 [0.28, 10.58], 0.5591		1.30 [0.35, 4.89], 0.6979	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		2.10 [0.21, 21.10], 0.5231		1.41 [0.26, 7.49], 0.6892	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		0.14 [-0.24, 0.53], 0.4670		0.06 [-0.22, 0.34], 0.6702	
Vist 13/ET:n/N1 (%)	7/18 (38.9)	1/5 (20.0)	15/32 (46.9)	1/5 (20.0)	22/50 (44.0)	2/10 (20.0)
RR [95%-CI]; p-value	1.94 [0.31, 12.32], 0.4802		2.34 [0.39, 14.06], 0.3514		2.20 [0.61, 7.90], 0.2267	
OR [95%-CI]; p-value	2.55 [0.23, 27.71], 0.4327		3.53 [0.35, 35.16], 0.2593		3.14 [0.61, 16.32], 0.1573	
RD [95%-CI]; p-value	0.19 [-0.23, 0.61], 0.3743		0.27 [-0.12, 0.66], 0.1778		0.24 [-0.04, 0.52], 0.0971	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
EAP:n/N2 (%)	44/108 (40.7)	5/63 (7.9)	38/98 (38.8)	4/61 (6.6)	82/206 (39.8)	9/124 (7.3)
RR [95%-CI]; p-value	5.13 [2.15, 12.27], 0.0002		5.91 [2.22, 15.75], 0.0004		5.48 [2.86, 10.52], <0.0001	
OR [95%-CI]; p-value	7.98 [2.96, 21.48], <0.0001		9.03 [3.03, 26.90], <0.0001		8.45 [4.06, 17.60], <0.0001	
RD [95%-CI]; p-value	0.33 [0.21, 0.44], <0.0001		0.32 [0.21, 0.44], <0.0001		0.33 [0.24, 0.41], <0.0001	
Vist 13/ET:n/N2 (%)	44/108 (40.7)	6/63 (9.5)	45/98 (45.9)	7/61 (11.5)	89/206 (43.2)	13/124 (10.5)
RR [95%-CI]; p-value	4.28 [1.93, 9.47], 0.0003		4.00 [1.93, 8.30], 0.0002		4.12 [2.41, 7.05], <0.0001	
OR [95%-CI]; p-value	6.53 [2.59, 16.47], <0.0001		6.55 [2.71, 15.82], <0.0001		6.50 [3.43, 12.28], <0.0001	
RD [95%-CI]; p-value	0.31 [0.19, 0.43], <0.0001		0.34 [0.22, 0.47], <0.0001		0.33 [0.24, 0.41], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.

Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).

Source: Listing 14.8.1

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_1_1_1_m_pth30pct_dose.sas using SAS 9.4

Table 12.2.1.1.2.s7

Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH

ITT Population

Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2239		0.5370		0.2221	
Vist 13/ET	0.8672		0.6172		0.7069	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
EAP:n/N1 (%)	10/18 (55.6)	2/5 (40.0)	23/32 (71.9)	2/5 (40.0)	33/50 (66.0)	4/10 (40.0)
RR [95%-CI]; p-value	1.39 [0.44, 4.39], 0.5757		1.80 [0.60, 5.37], 0.2943		1.65 [0.75, 3.62], 0.2110	
OR [95%-CI]; p-value	1.88 [0.25, 14.08], 0.5379		3.83 [0.55, 26.89], 0.1568		2.91 [0.72, 11.74], 0.1227	
RD [95%-CI]; p-value	0.16 [-0.33, 0.64], 0.5312		0.32 [-0.14, 0.78], 0.1714		0.26 [-0.07, 0.59], 0.1235	
Vist 13/ET:n/N1 (%)	8/18 (44.4)	1/5 (20.0)	23/32 (71.9)	2/5 (40.0)	31/50 (62.0)	3/10 (30.0)
RR [95%-CI]; p-value	2.22 [0.36, 13.82], 0.3918		1.80 [0.60, 5.37], 0.2943		2.07 [0.78, 5.46], 0.1430	
OR [95%-CI]; p-value	3.20 [0.30, 34.59], 0.3218		3.83 [0.55, 26.89], 0.1568		3.81 [0.88, 16.53], 0.0623	
RD [95%-CI]; p-value	0.24 [-0.17, 0.66], 0.2529		0.32 [-0.14, 0.78], 0.1714		0.32 [0.01, 0.63], 0.0460	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
EAP:n/N2 (%)	77/108 (71.3)	15/63 (23.8)	67/98 (68.4)	16/61 (26.2)	144/206 (69.9)	31/124 (25.0)
RR [95%-CI]; p-value	2.99 [1.89, 4.73], <0.0001		2.61 [1.68, 4.05], <0.0001		2.80 [2.03, 3.84], <0.0001	
OR [95%-CI]; p-value	7.95 [3.89, 16.23], <0.0001		6.08 [2.98, 12.39], <0.0001		6.97 [4.21, 11.53], <0.0001	
RD [95%-CI]; p-value	0.47 [0.34, 0.61], <0.0001		0.42 [0.28, 0.57], <0.0001		0.45 [0.35, 0.55], <0.0001	
Vist 13/ET:n/N2 (%)	76/108 (70.4)	17/63 (27.0)	70/98 (71.4)	18/61 (29.5)	146/206 (70.9)	35/124 (28.2)
RR [95%-CI]; p-value	2.61 [1.71, 3.99], <0.0001		2.42 [1.61, 3.64], <0.0001		2.51 [1.87, 3.37], <0.0001	
OR [95%-CI]; p-value	6.43 [3.21, 12.85], <0.0001		5.97 [2.96, 12.07], <0.0001		6.19 [3.78, 10.13], <0.0001	
RD [95%-CI]; p-value	0.43 [0.29, 0.57], <0.0001		0.42 [0.27, 0.56], <0.0001		0.43 [0.33, 0.53], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.

Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).

Source: Listing 14.8.1

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_2_1_1_2_m_pth10pct_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0820		0.7680		0.1983	
Comparison Baseline vs. EAP	0.2029		0.3947		0.1615	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	19.8 (5.14)	17.5 (6.97)	21.7 (5.64)	19.8 (5.56)	21.0 (5.49)	18.6 (6.07)
Visit 13/ET						
n/N1	17/18	5/5	30/32	4/5	47/50	9/10
Mean (SD)	49.9 (19.75)	18.8 (7.98)	61.5 (19.25)	18.5 (4.43)	57.3 (20.03)	18.7 (6.26)
EAP						
n/N1	14/18	5/5	30/32	4/5	44/50	9/10
Mean (SD)	54.0 (19.43)	20.0 (8.03)	61.7 (19.83)	16.9 (5.33)	59.2 (19.81)	18.6 (6.74)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	30.3 (3.96)	2.2 (7.35)	39.8 (3.18)	-3.8 (8.70)	35.2 (2.56)	-0.9 (5.66)
95% CI	[22.05, 38.63]	[-13.20, 17.56]	[33.31, 46.27]	[-21.59, 13.92]	[30.09, 40.37]	[-12.30, 10.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	28.16		43.63		36.16	
95% CI	[10.61, 45.70]		[24.73, 62.53]		[23.69, 48.63]	
p-value	0.0033		<0.0001		<0.0001	
Hedges' g	1.74		2.48		2.17	
95% CI	[0.65, 2.83]		[1.30, 3.65]		[1.36, 2.97]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	34.4 (3.96)	3.5 (6.66)	39.9 (3.23)	-1.6 (8.92)	37.4 (2.69)	1.1 (5.65)
95% CI	[26.02, 42.81]	[-10.62, 17.63]	[33.28, 46.46]	[-19.78, 16.61]	[31.96, 42.78]	[-10.26, 12.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	30.91		41.46		36.27	
95% CI	[14.41, 47.40]		[22.06, 60.85]		[23.69, 48.86]	
p-value	0.0011		0.0001		<0.0001	
Hedges' g	2.06		2.36		2.26	
95% CI	[0.88, 3.23]		[1.19, 3.52]		[1.44, 3.09]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	20.0 (5.05)	19.3 (5.46)	19.2 (5.35)	19.3 (5.74)	19.6 (5.20)	19.3 (5.58)
Visit 13/ET						
n/N2	106/108	62/63	94/98	56/61	200/206	118/124
Mean (SD)	69.8 (23.56)	17.3 (6.01)	70.3 (23.86)	20.0 (6.94)	70.0 (23.64)	18.6 (6.59)
EAP						
n/N2	104/108	59/63	94/98	57/61	198/206	116/124
Mean (SD)	68.8 (22.10)	17.5 (6.13)	68.4 (21.75)	19.6 (6.59)	68.6 (21.88)	18.5 (6.42)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.2.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.8 (1.81)	-2.1 (2.37)	51.1 (1.96)	0.5 (2.54)	50.5 (1.33)	-0.8 (1.73)
95% CI	[46.21, 53.36]	[-6.79, 2.56]	[47.28, 55.02]	[-4.55, 5.49]	[47.86, 53.09]	[-4.24, 2.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.90		50.68		51.31	
95% CI	[46.01, 57.79]		[44.34, 57.02]		[47.02, 55.60]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.78		2.67		2.73	
95% CI	[2.35, 3.21]		[2.22, 3.11]		[2.42, 3.05]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	48.9 (1.73)	-2.0 (2.30)	49.4 (1.74)	0.3 (2.24)	49.1 (1.23)	-0.9 (1.60)
95% CI	[45.49, 52.32]	[-6.58, 2.50]	[45.94, 52.83]	[-4.16, 4.70]	[46.71, 51.55]	[-4.01, 2.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.94		49.11		49.99	
95% CI	[45.26, 56.62]		[43.50, 54.73]		[46.01, 53.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.87		2.90		2.90	
95% CI	[2.43, 3.32]		[2.44, 3.36]		[2.57, 3.22]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_2_1_m_25d_dose.sas using SAS 9.4

Table 12.3.1.1.s7
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0384		0.9281		0.4237	
Vist 13/ET	0.4323		0.9753		0.8666	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
EAP:n/N1 (%)	13/18 (72.2)	1/5 (20.0)	29/32 (90.6)	0/5 (0.0)	42/50 (84.0)	1/10 (10.0)
RR [95%-CI]; p-value	3.61 [0.61, 21.33], 0.1565		9.97 [0.71, 140.42], 0.0884		8.40 [1.30, 54.14], 0.0252	
OR [95%-CI]; p-value	10.40 [0.92, 117.18], 0.0343		96.67 [4.18, 2235.00], <0.0001		47.25 [5.24, 426.43], <0.0001	
RD [95%-CI]; p-value	0.52 [0.12, 0.93], 0.0119		0.82 [0.55, 1.00], <0.0001		0.74 [0.53, 0.95], <0.0001	
Vist 13/ET:n/N1 (%)	14/18 (77.8)	0/5 (0.0)	29/32 (90.6)	0/5 (0.0)	43/50 (86.0)	0/10 (0.0)
RR [95%-CI]; p-value	8.56 [0.60, 121.62], 0.1130		9.97 [0.71, 140.42], 0.0884		18.06 [1.20, 270.70], 0.0362	
OR [95%-CI]; p-value	35.00 [1.56, 786.49], 0.0037		96.67 [4.18, 2235.00], <0.0001		122.86 [6.43, 2348.37], <0.0001	
RD [95%-CI]; p-value	0.69 [0.38, 0.99], <0.0001		0.82 [0.55, 1.00], <0.0001		0.81 [0.65, 0.97], <0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
EAP:n/N2 (%)	100/108 (92.6)	1/63 (1.6)	91/98 (92.9)	5/61 (8.2)	191/206 (92.7)	6/124 (4.8)
RR [95%-CI]; p-value	58.33 [8.34, 407.99], <0.0001		11.33 [4.88, 26.28], <0.0001		19.16 [8.77, 41.86], <0.0001	
OR [95%-CI]; p-value	775.00 [94.63, 6346.90], <0.0001		145.60 [44.08, 480.97], <0.0001		250.42 [94.54, 663.36], <0.0001	
RD [95%-CI]; p-value	0.91 [0.85, 0.97], <0.0001		0.85 [0.76, 0.93], <0.0001		0.88 [0.83, 0.93], <0.0001	
Vist 13/ET:n/N2 (%)	97/108 (89.8)	2/63 (3.2)	92/98 (93.9)	6/61 (9.8)	189/206 (91.7)	8/124 (6.5)
RR [95%-CI]; p-value	28.29 [7.22, 110.81], <0.0001		9.54 [4.46, 20.44], <0.0001		14.22 [7.27, 27.83], <0.0001	
OR [95%-CI]; p-value	268.95 [57.64, 1254.94], <0.0001		140.56 [43.20, 457.36], <0.0001		161.21 [67.43, 385.38], <0.0001	
RD [95%-CI]; p-value	0.87 [0.79, 0.94], <0.0001		0.84 [0.75, 0.93], <0.0001		0.85 [0.80, 0.91], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_3_1_1_m_25d30_dose.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4507		0.6994		0.3302	
Comparison Baseline vs. EAP	0.1890		0.4377		0.0769	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	159.5 (49.19)	133.2 (43.35)	146.4 (61.95)	145.3 (28.16)	153.2 (55.38)	138.7 (36.90)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	118.1 (45.55)	118.4 (38.66)	123.4 (135.49)	173.1 (78.69)	120.9 (101.88)	143.0 (64.61)
EAP						
n/N1	17/23	11/11	20/21	8/9	37/44	19/20
Mean (SD)	114.4 (50.40)	116.3 (41.44)	133.4 (128.28)	171.3 (59.47)	124.7 (99.53)	139.5 (55.73)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-38.4 (9.76)	-29.2 (13.00)	-23.2 (17.71)	28.3 (27.05)	-35.2 (11.71)	7.2 (16.67)
95% CI	[-58.43, -18.37]	[-55.87, -2.52]	[-59.49, 13.18]	[-27.20, 83.81]	[-58.71, -11.77]	[-26.19, 40.61]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-9.21		-51.46		-42.45	
95% CI	[-43.33, 24.92]		[-117.81, 14.88]		[-83.49, -1.40]	
p-value	0.5844		0.1231		0.0429	
Hedges' g	-0.58		-0.56		-0.52	
95% CI	[-1.31, 0.16]		[-1.33, 0.21]		[-1.06, 0.02]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-41.5 (10.81)	-28.0 (13.57)	-15.9 (16.67)	27.5 (26.36)	-32.2 (11.30)	5.0 (15.95)
95% CI	[-63.74, -19.21]	[-55.93, -0.04]	[-50.18, 18.47]	[-26.82, 81.75]	[-54.92, -9.54]	[-27.02, 37.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-13.49		-43.32		-37.23	
95% CI	[-49.95, 22.98]		[-107.56, 20.92]		[-76.69, 2.23]	
p-value	0.4534		0.1771		0.0639	
Hedges' g	-0.58		-0.50		-0.46	
95% CI	[-1.34, 0.17]		[-1.31, 0.30]		[-1.01, 0.10]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	144.4 (57.10)	143.8 (46.75)	147.8 (64.83)	157.0 (66.62)	146.1 (61.07)	150.5 (57.86)
Visit 13/ET						
n/N2	110/118	57/61	111/123	54/63	221/241	111/124
Mean (SD)	113.5 (64.39)	154.5 (67.99)	114.8 (80.16)	169.4 (84.74)	114.2 (72.58)	161.7 (76.61)
EAP						
n/N2	100/118	53/61	104/123	53/63	204/241	106/124
Mean (SD)	108.7 (51.25)	152.3 (67.72)	109.2 (61.80)	154.9 (65.93)	109.0 (56.74)	153.6 (66.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.2.1.s8
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.8 (4.71)	13.3 (6.55)	-29.7 (5.04)	9.4 (7.24)	-30.5 (3.45)	11.8 (4.88)
95% CI	[-40.12, -21.51]	[0.39, 26.24]	[-39.66, -19.77]	[-4.86, 23.74]	[-37.28, -23.69]	[2.24, 21.43]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.13		-39.16		-42.32	
95% CI	[-60.06, -28.20]		[-56.63, -21.69]		[-54.09, -30.56]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.89		-0.73		-0.81	
95% CI	[-1.22, -0.56]		[-1.06, -0.39]		[-1.05, -0.57]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.5 (3.98)	13.2 (5.46)	-32.7 (3.61)	2.0 (5.06)	-32.5 (2.68)	7.5 (3.71)
95% CI	[-40.36, -24.64]	[2.44, 24.04]	[-39.78, -25.53]	[-8.05, 11.96]	[-37.82, -27.28]	[0.22, 14.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.74		-34.61		-40.08	
95% CI	[-59.10, -32.39]		[-46.92, -22.30]		[-49.09, -31.07]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.14		-0.85		-1.00	
95% CI	[-1.50, -0.79]		[-1.19, -0.51]		[-1.25, -0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_2_1_m_pth_vitd.sas using SAS 9.4

Table 12.2.1.1.1.s8
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0182		0.6402		0.2245	
Vist 13/ET	0.3477		0.4785		0.8636	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
EAP:n/N1 (%)	6/23 (26.1)	3/11 (27.3)	9/21 (42.9)	0/9 (0.0)	15/44 (34.1)	3/20 (15.0)
RR [95%-CI]; p-value	0.96 [0.29, 3.13], 0.9414		8.14 [0.52, 126.45], 0.1340		2.27 [0.74, 6.97], 0.1513	
OR [95%-CI]; p-value	0.94 [0.19, 4.76], 0.9416		13.50 [0.69, 264.73], 0.0379		2.93 [0.74, 11.61], 0.1154	
RD [95%-CI]; p-value	-0.01 [-0.33, 0.31], 0.9418		0.38 [0.12, 0.63], 0.0038		0.19 [-0.02, 0.40], 0.0748	
Vist 13/ET:n/N1 (%)	9/23 (39.1)	2/11 (18.2)	10/21 (47.6)	0/9 (0.0)	19/44 (43.2)	2/20 (10.0)
RR [95%-CI]; p-value	2.15 [0.56, 8.33], 0.2670		9.05 [0.59, 139.41], 0.1145		4.32 [1.11, 16.79], 0.0347	
OR [95%-CI]; p-value	2.89 [0.50, 16.58], 0.2219		16.36 [0.84, 320.15], 0.0226		6.84 [1.41, 33.14], 0.0088	
RD [95%-CI]; p-value	0.21 [-0.09, 0.51], 0.1752		0.42 [0.17, 0.68], 0.0012		0.33 [0.14, 0.53], 0.0009	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
EAP:n/N2 (%)	40/118 (33.9)	3/61 (4.9)	40/123 (32.5)	5/63 (7.9)	80/241 (33.2)	8/124 (6.5)
RR [95%-CI]; p-value	6.89 [2.22, 21.38], 0.0008		4.10 [1.70, 9.87], 0.0017		5.15 [2.57, 10.30], <0.0001	
OR [95%-CI]; p-value	9.91 [2.92, 33.63], <0.0001		5.59 [2.08, 15.02], 0.0002		7.20 [3.35, 15.48], <0.0001	
RD [95%-CI]; p-value	0.29 [0.19, 0.39], <0.0001		0.25 [0.14, 0.35], <0.0001		0.27 [0.19, 0.34], <0.0001	
Vist 13/ET:n/N2 (%)	45/118 (38.1)	5/61 (8.2)	51/123 (41.5)	8/63 (12.7)	96/241 (39.8)	13/124 (10.5)
RR [95%-CI]; p-value	4.65 [1.95, 11.11], 0.0005		3.27 [1.65, 6.45], 0.0007		3.80 [2.22, 6.50], <0.0001	
OR [95%-CI]; p-value	6.90 [2.57, 18.53], <0.0001		4.87 [2.14, 11.10], <0.0001		5.65 [3.01, 10.61], <0.0001	
RD [95%-CI]; p-value	0.30 [0.19, 0.41], <0.0001		0.29 [0.17, 0.41], <0.0001		0.29 [0.21, 0.38], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_1_1_1_m_pth30pct_vitd.sas using SAS 9.4

Table 12.2.1.1.2.s8
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.2090		0.7585		0.5104	
Vist 13/ET	0.0438		0.9697		0.1730	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
EAP:n/N1 (%)	13/23 (56.5)	4/11 (36.4)	14/21 (66.7)	2/9 (22.2)	27/44 (61.4)	6/20 (30.0)
RR [95%-CI]; p-value	1.55 [0.66, 3.67], 0.3148		3.00 [0.85, 10.57], 0.0872		2.05 [1.01, 4.16], 0.0480	
OR [95%-CI]; p-value	2.28 [0.52, 9.99], 0.2714		7.00 [1.14, 42.97], 0.0253		3.71 [1.19, 11.50], 0.0200	
RD [95%-CI]; p-value	0.20 [-0.15, 0.55], 0.2577		0.44 [0.11, 0.78], 0.0100		0.31 [0.07, 0.56], 0.0128	
Vist 13/ET:n/N1 (%)	12/23 (52.2)	5/11 (45.5)	17/21 (81.0)	3/9 (33.3)	29/44 (65.9)	8/20 (40.0)
RR [95%-CI]; p-value	1.15 [0.54, 2.45], 0.7209		2.43 [0.94, 6.26], 0.0663		1.65 [0.93, 2.93], 0.0900	
OR [95%-CI]; p-value	1.31 [0.31, 5.53], 0.7139		8.50 [1.46, 49.54], 0.0112		2.90 [0.97, 8.63], 0.0517	
RD [95%-CI]; p-value	0.07 [-0.29, 0.43], 0.7131		0.48 [0.13, 0.83], 0.0078		0.26 [0.00, 0.52], 0.0476	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
EAP:n/N2 (%)	74/118 (62.7)	13/61 (21.3)	76/123 (61.8)	16/63 (25.4)	150/241 (62.2)	29/124 (23.4)
RR [95%-CI]; p-value	2.94 [1.78, 4.86], <0.0001		2.43 [1.56, 3.80], <0.0001		2.66 [1.91, 3.71], <0.0001	
OR [95%-CI]; p-value	6.21 [3.03, 12.73], <0.0001		4.75 [2.42, 9.32], <0.0001		5.40 [3.31, 8.82], <0.0001	
RD [95%-CI]; p-value	0.41 [0.28, 0.55], <0.0001		0.36 [0.23, 0.50], <0.0001		0.39 [0.29, 0.48], <0.0001	
Vist 13/ET:n/N2 (%)	78/118 (66.1)	14/61 (23.0)	79/123 (64.2)	17/63 (27.0)	157/241 (65.1)	31/124 (25.0)
RR [95%-CI]; p-value	2.88 [1.79, 4.64], <0.0001		2.38 [1.55, 3.65], <0.0001		2.61 [1.89, 3.58], <0.0001	
OR [95%-CI]; p-value	6.55 [3.22, 13.29], <0.0001		4.86 [2.49, 9.47], <0.0001		5.61 [3.45, 9.11], <0.0001	
RD [95%-CI]; p-value	0.43 [0.30, 0.57], <0.0001		0.37 [0.23, 0.51], <0.0001		0.40 [0.30, 0.50], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_2_1_1_2_m_pth10pct_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8392		0.5143		0.6359	
Comparison Baseline vs. EAP	0.2275		0.5435		0.1642	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	21.7 (5.12)	18.5 (4.57)	20.7 (4.91)	23.7 (4.18)	21.2 (4.99)	20.9 (5.05)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	64.5 (20.49)	21.2 (7.31)	68.1 (20.53)	26.9 (4.26)	66.4 (20.33)	23.8 (6.65)
EAP						
n/N1	17/23	11/11	20/21	8/9	37/44	19/20
Mean (SD)	65.1 (13.25)	21.6 (6.99)	66.4 (17.66)	26.4 (3.47)	65.8 (15.59)	23.6 (6.13)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	43.3 (4.05)	1.2 (5.41)	47.5 (3.77)	2.9 (5.86)	45.0 (2.70)	2.9 (3.84)
95% CI	[35.00, 51.61]	[-9.87, 12.33]	[39.77, 55.23]	[-9.08, 14.97]	[39.58, 50.41]	[-4.79, 10.58]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.08		44.56		42.10	
95% CI	[27.82, 56.34]		[29.99, 59.12]		[32.69, 51.50]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.25		2.58		2.48	
95% CI	[1.33, 3.17]		[1.57, 3.58]		[1.79, 3.17]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	43.7 (2.77)	2.2 (3.49)	46.0 (3.13)	1.9 (5.04)	44.4 (2.09)	2.9 (2.93)
95% CI	[37.96, 49.38]	[-5.01, 9.36]	[39.57, 52.48]	[-8.49, 12.26]	[40.20, 48.57]	[-2.97, 8.81]
Diff in LS-Mean [ER-Calcifediol - Placebo]	41.50		44.14		41.46	
95% CI	[32.05, 50.94]		[31.73, 56.55]		[34.24, 48.69]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.48		3.04		3.32	
95% CI	[2.31, 4.65]		[1.91, 4.17]		[2.50, 4.15]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	19.9 (5.04)	19.4 (5.60)	19.5 (5.66)	18.7 (5.42)	19.7 (5.36)	19.1 (5.50)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	65.2 (25.33)	16.8 (5.75)	65.2 (25.32)	18.7 (6.34)	65.2 (25.27)	17.7 (6.09)
EAP						
n/N2	101/118	53/61	104/123	53/63	205/241	106/124
Mean (SD)	67.4 (23.46)	16.8 (5.82)	66.8 (22.14)	18.4 (6.22)	67.1 (22.75)	17.6 (6.05)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.2.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.5 (1.92)	-2.6 (2.70)	45.8 (1.98)	-0.5 (2.86)	45.6 (1.38)	-1.6 (1.96)
95% CI	[41.65, 49.25]	[-7.92, 2.73]	[41.92, 49.72]	[-6.18, 5.11]	[42.93, 48.34]	[-5.43, 2.29]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.05		46.35		47.20	
95% CI	[41.51, 54.59]		[39.49, 53.21]		[42.49, 51.92]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.36		2.22		2.30	
95% CI	[1.95, 2.76]		[1.81, 2.62]		[2.01, 2.59]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.9 (1.85)	-2.6 (2.56)	47.4 (1.75)	-0.4 (2.45)	47.6 (1.27)	-1.5 (1.77)
95% CI	[44.22, 51.55]	[-7.66, 2.45]	[43.96, 50.88]	[-5.22, 4.48]	[45.14, 50.15]	[-4.95, 2.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.49		47.79		49.11	
95% CI	[44.25, 56.74]		[41.82, 53.75]		[44.82, 53.40]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.70		2.66		2.70	
95% CI	[2.26, 3.15]		[2.22, 3.11]		[2.38, 3.01]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_2_1_m_25d_vitd.sas using SAS 9.4

Table 12.3.1.1.s8
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.0391		0.0874		0.0038	
Vist 13/ET	0.0406		0.0137		0.0009	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
EAP:n/N1 (%)	17/23 (73.9)	2/11 (18.2)	19/21 (90.5)	2/9 (22.2)	36/44 (81.8)	4/20 (20.0)
RR [95%-CI]; p-value	4.07 [1.13, 14.58], 0.0313		4.07 [1.19, 13.93], 0.0253		4.09 [1.68, 9.94], 0.0019	
OR [95%-CI]; p-value	12.75 [2.12, 76.57], 0.0022		33.25 [3.90, 283.45], 0.0002		18.00 [4.73, 68.53], <0.0001	
RD [95%-CI]; p-value	0.56 [0.27, 0.85], 0.0002		0.68 [0.38, 0.98], <0.0001		0.62 [0.41, 0.83], <0.0001	
Vist 13/ET:n/N1 (%)	18/23 (78.3)	2/11 (18.2)	20/21 (95.2)	3/9 (33.3)	38/44 (86.4)	5/20 (25.0)
RR [95%-CI]; p-value	4.30 [1.21, 15.36], 0.0245		2.86 [1.13, 7.23], 0.0267		3.45 [1.60, 7.45], 0.0016	
OR [95%-CI]; p-value	16.20 [2.61, 100.45], 0.0009		40.00 [3.49, 458.98], 0.0002		19.00 [5.03, 71.75], <0.0001	
RD [95%-CI]; p-value	0.60 [0.32, 0.88], <0.0001		0.62 [0.30, 0.94], 0.0002		0.61 [0.40, 0.83], <0.0001	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
EAP:n/N2 (%)	96/118 (81.4)	0/61 (0.0)	101/123 (82.1)	3/63 (4.8)	197/241 (81.7)	3/124 (2.4)
RR [95%-CI]; p-value	100.07 [6.32, 1584.01], 0.0011		17.24 [5.70, 52.19], <0.0001		33.79 [11.03, 103.49], <0.0001	
OR [95%-CI]; p-value	532.36 [31.69, 8944.25], <0.0001		91.82 [26.36, 319.79], <0.0001		180.58 [54.87, 594.33], <0.0001	
RD [95%-CI]; p-value	0.81 [0.73, 0.88], <0.0001		0.77 [0.69, 0.86], <0.0001		0.79 [0.74, 0.85], <0.0001	
Vist 13/ET:n/N2 (%)	99/118 (83.9)	0/61 (0.0)	103/123 (83.7)	3/63 (4.8)	202/241 (83.8)	3/124 (2.4)
RR [95%-CI]; p-value	103.19 [6.52, 1633.15], 0.0010		17.59 [5.81, 53.20], <0.0001		34.64 [11.31, 106.09], <0.0001	
OR [95%-CI]; p-value	635.68 [37.66, 10730.10], <0.0001		103.00 [29.38, 361.14], <0.0001		208.91 [63.19, 690.63], <0.0001	
RD [95%-CI]; p-value	0.83 [0.76, 0.90], <0.0001		0.79 [0.71, 0.87], <0.0001		0.81 [0.76, 0.87], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_3_1_1_m_25d30_vitd.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6914		0.1928		0.4282	
Comparison Baseline vs. EAP	0.4637		0.0814		0.4060	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	149.7 (58.01)	143.8 (50.79)	161.8 (74.90)	161.2 (63.22)	155.8 (67.14)	152.0 (57.30)
Visit 13/ET						
n/N1	63/68	38/40	65/70	29/36	128/138	67/76
Mean (SD)	118.7 (66.92)	155.2 (69.67)	134.0 (115.53)	177.4 (83.13)	126.5 (94.72)	164.8 (76.00)
EAP						
n/N1	59/68	36/40	61/70	30/36	120/138	66/76
Mean (SD)	108.7 (50.93)	150.5 (70.60)	128.4 (99.48)	159.4 (62.15)	118.7 (79.70)	154.5 (66.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.4 (6.28)	11.7 (8.09)	-28.0 (8.89)	8.8 (13.31)	-30.0 (5.45)	10.8 (7.60)
95% CI	[-43.87, -18.95]	[-4.35, 27.76]	[-45.66, -10.35]	[-17.62, 35.26]	[-40.75, -19.27]	[-4.15, 25.81]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.11		-36.83		-40.84	
95% CI	[-63.46, -22.77]		[-68.63, -5.02]		[-59.28, -22.40]	
p-value	<0.0001		0.0237		<0.0001	
Hedges' g	-0.87		-0.52		-0.67	
95% CI	[-1.29, -0.46]		[-0.96, -0.08]		[-0.97, -0.37]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.6 (5.55)	10.4 (7.11)	-30.1 (7.27)	-1.3 (10.36)	-33.4 (4.56)	4.7 (6.17)
95% CI	[-47.62, -25.58]	[-3.71, 24.52]	[-44.59, -15.70]	[-21.94, 19.25]	[-42.42, -24.43]	[-7.52, 16.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-47.00		-28.80		-38.08	
95% CI	[-64.93, -29.08]		[-53.95, -3.65]		[-53.22, -22.94]	
p-value	<0.0001		0.0253		<0.0001	
Hedges' g	-1.11		-0.50		-0.77	
95% CI	[-1.55, -0.67]		[-0.94, -0.06]		[-1.08, -0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	144.2 (54.34)	140.2 (40.22)	134.2 (48.98)	149.9 (63.34)	139.1 (51.77)	145.4 (53.55)
Visit 13/ET						
n/N2	66/73	30/32	67/74	34/36	133/147	64/68
Mean (SD)	109.9 (56.77)	140.3 (59.46)	98.9 (52.26)	163.5 (84.15)	104.3 (54.62)	152.6 (73.97)
EAP						
n/N2	58/73	28/32	63/74	31/36	121/147	59/68
Mean (SD)	110.4 (51.41)	140.5 (58.18)	98.3 (38.95)	154.8 (68.39)	104.1 (45.56)	148.0 (63.61)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.2.1.s9
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-33.7 (6.03)	2.5 (8.95)	-29.0 (5.66)	14.3 (8.01)	-32.2 (4.17)	10.3 (6.03)
95% CI	[-45.62, -21.69]	[-15.30, 20.24]	[-40.24, -17.78]	[-1.54, 30.23]	[-40.46, -24.01]	[-1.58, 22.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-36.13		-43.36		-42.54	
95% CI	[-57.59, -14.67]		[-63.02, -23.70]		[-57.01, -28.07]	
p-value	0.0012		<0.0001		<0.0001	
Hedges' g	-0.75		-0.93		-0.84	
95% CI	[-1.19, -0.31]		[-1.35, -0.50]		[-1.15, -0.53]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.2 (5.34)	3.3 (7.69)	-29.4 (4.36)	11.0 (6.25)	-31.1 (3.42)	7.9 (4.90)
95% CI	[-42.84, -21.60]	[-12.00, 18.61]	[-38.03, -20.72]	[-1.46, 23.39]	[-37.85, -24.36]	[-1.78, 17.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.53		-40.34		-39.00	
95% CI	[-54.18, -16.88]		[-55.62, -25.06]		[-50.80, -27.20]	
p-value	0.0003		<0.0001		<0.0001	
Hedges' g	-0.87		-1.07		-0.96	
95% CI	[-1.33, -0.40]		[-1.52, -0.61]		[-1.29, -0.64]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_2_1_m_pth_bl25d.sas using SAS 9.4

Table 12.2.1.1.1.s9
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.6413		0.1080		0.2217	
Vist 13/ET	0.4421		0.3884		0.9280	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
EAP:n/N1 (%)	24/68 (35.3)	3/40 (7.5)	23/70 (32.9)	5/36 (13.9)	47/138 (34.1)	8/76 (10.5)
RR [95%-CI]; p-value	4.71 [1.51, 14.64], 0.0075		2.37 [0.98, 5.70], 0.0550		3.24 [1.61, 6.49], 0.0009	
OR [95%-CI]; p-value	6.73 [1.88, 24.13], 0.0013		3.03 [1.04, 8.83], 0.0359		4.39 [1.95, 9.90], 0.0002	
RD [95%-CI]; p-value	0.28 [0.14, 0.42], <0.0001		0.19 [0.03, 0.35], 0.0184		0.24 [0.13, 0.34], <0.0001	
Vist 13/ET:n/N1 (%)	27/68 (39.7)	3/40 (7.5)	28/70 (40.0)	5/36 (13.9)	55/138 (39.9)	8/76 (10.5)
RR [95%-CI]; p-value	5.29 [1.72, 16.34], 0.0038		2.88 [1.22, 6.82], 0.0162		3.79 [1.91, 7.52], 0.0001	
OR [95%-CI]; p-value	8.12 [2.27, 29.01], 0.0003		4.13 [1.43, 11.91], 0.0060		5.63 [2.51, 12.64], <0.0001	
RD [95%-CI]; p-value	0.32 [0.18, 0.46], <0.0001		0.26 [0.10, 0.42], 0.0015		0.29 [0.19, 0.40], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
EAP:n/N2 (%)	22/73 (30.1)	3/32 (9.4)	26/74 (35.1)	0/36 (0.0)	48/147 (32.7)	3/68 (4.4)
RR [95%-CI]; p-value	3.21 [1.04, 9.98], 0.0433		25.65 [1.61, 409.36], 0.0217		7.40 [2.39, 22.92], 0.0005	
OR [95%-CI]; p-value	4.17 [1.15, 15.14], 0.0215		39.00 [2.30, 661.87], <0.0001		10.51 [3.14, 35.15], <0.0001	
RD [95%-CI]; p-value	0.21 [0.06, 0.35], 0.0053		0.34 [0.22, 0.45], <0.0001		0.28 [0.19, 0.37], <0.0001	
Vist 13/ET:n/N2 (%)	27/73 (37.0)	4/32 (12.5)	33/74 (44.6)	3/36 (8.3)	60/147 (40.8)	7/68 (10.3)
RR [95%-CI]; p-value	2.96 [1.13, 7.76], 0.0275		5.35 [1.76, 16.28], 0.0031		3.97 [1.91, 8.21], 0.0002	
OR [95%-CI]; p-value	4.11 [1.30, 12.98], 0.0113		8.85 [2.49, 31.45], 0.0001		6.01 [2.57, 14.04], <0.0001	
RD [95%-CI]; p-value	0.24 [0.09, 0.40], 0.0026		0.36 [0.22, 0.51], <0.0001		0.31 [0.20, 0.41], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_1_1_1_m_pth30pct_bl25d.sas using SAS 9.4

Table 12.2.1.1.2.s9
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.6538		0.8554		0.8487	
Vist 13/ET	0.5203		0.7435		0.4886	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
EAP:n/N1 (%)	44/68 (64.7)	9/40 (22.5)	47/70 (67.1)	10/36 (27.8)	91/138 (65.9)	19/76 (25.0)
RR [95%-CI]; p-value	2.88 [1.58, 5.25], 0.0006		2.42 [1.39, 4.20], 0.0017		2.64 [1.75, 3.96], <0.0001	
OR [95%-CI]; p-value	6.31 [2.58, 15.43], <0.0001		5.31 [2.20, 12.85], 0.0001		5.81 [3.10, 10.88], <0.0001	
RD [95%-CI]; p-value	0.42 [0.25, 0.59], <0.0001		0.39 [0.21, 0.58], <0.0001		0.41 [0.28, 0.53], <0.0001	
Vist 13/ET:n/N1 (%)	42/68 (61.8)	9/40 (22.5)	45/70 (64.3)	9/36 (25.0)	87/138 (63.0)	18/76 (23.7)
RR [95%-CI]; p-value	2.75 [1.50, 5.03], 0.0011		2.57 [1.42, 4.65], 0.0018		2.66 [1.74, 4.06], <0.0001	
OR [95%-CI]; p-value	5.56 [2.29, 13.53], <0.0001		5.40 [2.20, 13.27], 0.0001		5.50 [2.92, 10.34], <0.0001	
RD [95%-CI]; p-value	0.39 [0.22, 0.57], <0.0001		0.39 [0.21, 0.57], <0.0001		0.39 [0.27, 0.52], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
EAP:n/N2 (%)	43/73 (58.9)	8/32 (25.0)	43/74 (58.1)	8/36 (22.2)	86/147 (58.5)	16/68 (23.5)
RR [95%-CI]; p-value	2.36 [1.25, 4.42], 0.0077		2.61 [1.38, 4.96], 0.0033		2.49 [1.59, 3.90], <0.0001	
OR [95%-CI]; p-value	4.30 [1.70, 10.86], 0.0014		4.85 [1.95, 12.08], 0.0004		4.58 [2.39, 8.77], <0.0001	
RD [95%-CI]; p-value	0.34 [0.15, 0.53], 0.0004		0.36 [0.18, 0.54], <0.0001		0.35 [0.22, 0.48], <0.0001	
Vist 13/ET:n/N2 (%)	48/73 (65.8)	10/32 (31.3)	51/74 (68.9)	11/36 (30.6)	99/147 (67.3)	21/68 (30.9)
RR [95%-CI]; p-value	2.10 [1.23, 3.61], 0.0069		2.26 [1.35, 3.78], 0.0020		2.18 [1.50, 3.17], <0.0001	
OR [95%-CI]; p-value	4.22 [1.73, 10.29], 0.0011		5.04 [2.13, 11.95], 0.0001		4.62 [2.49, 8.57], <0.0001	
RD [95%-CI]; p-value	0.35 [0.15, 0.54], 0.0005		0.38 [0.20, 0.57], <0.0001		0.36 [0.23, 0.50], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_2_1_1_2_m_pth10pct_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4799		0.0193		0.0338	
Comparison Baseline vs. EAP	0.0849		0.1986		0.0341	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	15.7 (2.57)	15.3 (3.08)	14.9 (3.23)	15.0 (3.42)	15.3 (2.94)	15.1 (3.23)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	60.1 (25.41)	14.7 (4.91)	60.9 (27.92)	16.3 (6.12)	60.5 (26.60)	15.4 (5.47)
EAP						
n/N1	60/68	36/40	61/70	30/36	121/138	66/76
Mean (SD)	62.6 (24.64)	14.6 (4.99)	61.1 (22.05)	15.9 (5.42)	61.9 (23.28)	15.2 (5.19)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.5 (2.54)	-0.5 (3.31)	45.9 (2.93)	1.3 (4.46)	45.2 (1.93)	0.4 (2.73)
95% CI	[39.49, 49.59]	[-7.06, 6.05]	[40.11, 51.75]	[-7.60, 10.14]	[41.43, 49.04]	[-5.01, 5.76]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.05		44.66		44.86	
95% CI	[36.76, 53.34]		[34.05, 55.27]		[38.27, 51.46]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.21		1.89		2.06	
95% CI	[1.71, 2.71]		[1.37, 2.40]		[1.70, 2.42]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.1 (2.52)	-0.5 (3.26)	46.1 (2.35)	1.1 (3.35)	46.6 (1.72)	0.3 (2.34)
95% CI	[42.07, 52.10]	[-6.97, 5.98]	[41.46, 50.78]	[-5.60, 7.71]	[43.22, 50.01]	[-4.35, 4.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.58		45.07		46.35	
95% CI	[39.38, 55.77]		[36.94, 53.19]		[40.61, 52.08]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.43		2.45		2.46	
95% CI	[1.90, 2.97]		[1.88, 3.01]		[2.07, 2.85]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	24.4 (2.61)	24.2 (3.10)	24.1 (2.99)	23.8 (3.17)	24.3 (2.80)	24.0 (3.12)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	69.9 (23.03)	21.1 (5.78)	70.3 (19.94)	22.8 (5.77)	70.1 (21.46)	22.0 (5.79)
EAP						
n/N2	58/73	28/32	63/74	31/36	121/147	59/68
Mean (SD)	71.6 (18.62)	21.5 (5.57)	72.2 (19.43)	22.9 (5.56)	71.9 (18.97)	22.3 (5.56)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.2.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.5 (2.39)	-3.3 (3.57)	46.3 (2.04)	-1.2 (2.86)	45.9 (1.56)	-2.2 (2.27)
95% CI	[40.72, 50.20]	[-10.37, 3.81]	[42.22, 50.31]	[-6.84, 4.53]	[42.78, 48.95]	[-6.69, 2.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.74		47.41		48.09	
95% CI	[40.21, 57.27]		[40.43, 54.40]		[42.66, 53.52]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.48		2.80		2.64	
95% CI	[1.92, 3.03]		[2.23, 3.36]		[2.24, 3.03]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.2 (2.06)	-2.9 (2.97)	48.1 (2.05)	-1.0 (2.93)	47.7 (1.45)	-2.0 (2.08)
95% CI	[43.12, 51.33]	[-8.82, 3.00]	[44.07, 52.22]	[-6.81, 4.82]	[44.83, 50.56]	[-6.06, 2.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.13		49.14		49.65	
95% CI	[42.94, 57.33]		[42.03, 56.24]		[44.64, 54.66]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.17		2.99		3.10	
95% CI	[2.52, 3.82]		[2.38, 3.59]		[2.65, 3.55]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_2_1_m_25d_bl25d.sas using SAS 9.4

Table 12.3.1.1.s9
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
EAP	0.8630		0.2094		0.2098	
Vist 13/ET	0.3256		0.1479		0.0602	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
EAP:n/N1 (%)	55/68 (80.9)	1/40 (2.5)	58/70 (82.9)	1/36 (2.8)	113/138 (81.9)	2/76 (2.6)
RR [95%-CI]; p-value	32.35 [4.66, 224.86], 0.0004		29.83 [4.31, 206.63], 0.0006		31.12 [7.91, 122.43], <0.0001	
OR [95%-CI]; p-value	165.00 [20.72, 1314.05], <0.0001		169.17 [21.08, 1357.73], <0.0001		167.24 [38.46, 727.22], <0.0001	
RD [95%-CI]; p-value	0.78 [0.68, 0.89], <0.0001		0.80 [0.70, 0.90], <0.0001		0.79 [0.72, 0.87], <0.0001	
Vist 13/ET:n/N1 (%)	54/68 (79.4)	0/40 (0.0)	58/70 (82.9)	1/36 (2.8)	112/138 (81.2)	1/76 (1.3)
RR [95%-CI]; p-value	64.32 [4.08, 1013.56], 0.0031		29.83 [4.31, 206.63], 0.0006		61.68 [8.79, 432.97], <0.0001	
OR [95%-CI]; p-value	308.57 [17.84, 5336.37], <0.0001		169.17 [21.08, 1357.73], <0.0001		323.08 [42.92, 2432.04], <0.0001	
RD [95%-CI]; p-value	0.78 [0.68, 0.88], <0.0001		0.80 [0.70, 0.90], <0.0001		0.80 [0.73, 0.87], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
EAP:n/N2 (%)	58/73 (79.5)	1/32 (3.1)	62/74 (83.8)	4/36 (11.1)	120/147 (81.6)	5/68 (7.4)
RR [95%-CI]; p-value	25.42 [3.68, 175.62], 0.0010		7.54 [2.98, 19.10], <0.0001		11.10 [4.76, 25.90], <0.0001	
OR [95%-CI]; p-value	119.87 [15.12, 950.57], <0.0001		41.33 [12.33, 138.52], <0.0001		56.00 [20.56, 152.49], <0.0001	
RD [95%-CI]; p-value	0.76 [0.65, 0.87], <0.0001		0.73 [0.59, 0.86], <0.0001		0.74 [0.65, 0.83], <0.0001	
Vist 13/ET:n/N2 (%)	63/73 (86.3)	2/32 (6.3)	65/74 (87.8)	5/36 (13.9)	128/147 (87.1)	7/68 (10.3)
RR [95%-CI]; p-value	13.81 [3.60, 53.00], 0.0001		6.32 [2.79, 14.33], <0.0001		8.46 [4.18, 17.11], <0.0001	
OR [95%-CI]; p-value	94.50 [19.48, 458.43], <0.0001		44.78 [13.84, 144.84], <0.0001		58.71 [23.43, 147.12], <0.0001	
RD [95%-CI]; p-value	0.80 [0.69, 0.92], <0.0001		0.74 [0.60, 0.87], <0.0001		0.77 [0.68, 0.86], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_3_1_1_m_25d30_bl25d.sas using SAS 9.4

Nachberechnungsdokument Subgruppenanalyse - Wirksamkeitsendpunkte (PP-Population)

Folgende Daten werden für die PP-Population

iPTH

- Absolute Veränderung des iPTH-Spiegels (pg/ml) im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 30 % im Plasma
- Anteil Patienten mit einer Reduktion des iPTH-Spiegels ≥ 10 % im Plasma

25(OH)D

- Absolute Veränderung des 25(OH)D-Spiegels (ng/ml) im Serum
- Anteil Patienten mit einem 25(OH)D-Spiegel ≥ 30 ng/ml im Serum

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1743		0.1781		0.0503	
Comparison Baseline vs. EAP	0.6457		0.0333		0.0566	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	147.1 (52.84)	134.4 (40.44)	159.0 (73.62)	165.2 (72.95)	152.3 (62.73)	149.3 (59.87)
Visit 13/ET						
n/N1	51/51	28/28	39/40	25/26	90/91	53/54
Mean (SD)	119.1 (62.78)	142.9 (58.99)	120.9 (109.46)	169.8 (84.55)	119.9 (85.62)	155.6 (72.74)
EAP						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	113.6 (49.12)	145.5 (61.37)	128.1 (100.34)	157.6 (74.90)	120.0 (75.87)	151.3 (67.84)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-26.4 (7.43)	5.6 (10.05)	-38.5 (12.33)	5.2 (15.40)	-32.7 (6.90)	6.3 (8.92)
95% CI	[-41.24, -11.65]	[-14.44, 25.59]	[-63.15, -13.85]	[-25.59, 35.99]	[-46.33, -19.05]	[-11.31, 23.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-32.02		-43.70		-39.02	
95% CI	[-57.00, -7.04]		[-83.15, -4.24]		[-61.32, -16.72]	
p-value	0.0127		0.0305		0.0007	
Hedges' g	-0.65		-0.55		-0.59	
95% CI	[-1.12, -0.19]		[-1.06, -0.05]		[-0.94, -0.25]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.0 (6.07)	8.3 (8.21)	-31.0 (9.55)	-7.4 (11.84)	-31.9 (5.51)	1.5 (7.10)
95% CI	[-44.07, -19.91]	[-8.06, 24.63]	[-50.12, -11.96]	[-31.06, 16.27]	[-42.79, -21.02]	[-12.54, 15.54]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.27		-23.65		-33.41	
95% CI	[-60.67, -19.88]		[-54.06, 6.76]		[-51.17, -15.64]	
p-value	0.0002		0.1252		0.0003	
Hedges' g	-0.96		-0.38		-0.65	
95% CI	[-1.44, -0.48]		[-0.88, 0.11]		[-0.99, -0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	142.3 (51.38)	138.9 (42.58)	134.8 (54.49)	145.3 (44.52)	138.1 (53.07)	142.1 (43.35)
Visit 13/ET						
n/N2	63/64	33/34	78/79	33/34	141/143	66/68
Mean (SD)	108.5 (60.95)	153.7 (73.08)	105.8 (76.01)	163.8 (69.84)	107.0 (69.46)	158.7 (71.11)
EAP						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	106.2 (53.29)	147.4 (70.76)	106.9 (62.66)	158.6 (57.09)	106.5 (58.45)	153.0 (64.06)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-33.5 (5.86)	17.6 (8.11)	-28.9 (5.26)	17.0 (8.10)	-31.4 (3.94)	17.7 (5.72)
95% CI	[-45.18, -21.90]	[1.50, 33.69]	[-39.37, -18.52]	[0.91, 33.03]	[-39.21, -23.68]	[6.42, 28.99]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-51.13		-45.92		-49.15	
95% CI	[-71.02, -31.25]		[-65.10, -26.74]		[-62.85, -35.46]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.10		-1.01		-1.06	
95% CI	[-1.55, -0.65]		[-1.43, -0.58]		[-1.37, -0.75]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.0 (4.98)	8.3 (6.83)	-28.1 (4.25)	13.9 (6.49)	-32.1 (3.25)	11.1 (4.68)
95% CI	[-45.93, -26.17]	[-5.28, 21.84]	[-36.56, -19.73]	[1.03, 26.73]	[-38.49, -25.69]	[1.87, 20.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.33		-42.02		-43.19	
95% CI	[-61.11, -27.55]		[-57.42, -26.63]		[-54.43, -31.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.11		-1.09		-1.10	
95% CI	[-1.55, -0.67]		[-1.51, -0.66]		[-1.40, -0.79]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_2_1_m_pth_age_pp.sas using SAS 9.4

Table 12.2.1.1.1.s1.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4787		0.0534		0.1302	
Vist 13/ET	0.5997		0.1129		0.1144	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
EAP:n/N1 (%)	16/51 (31.4)	1/28 (3.6)	13/40 (32.5)	5/26 (19.2)	29/91 (31.9)	6/54 (11.1)
RR [95%-CI]; p-value	8.78 [1.23, 62.80], 0.0304		1.69 [0.68, 4.18], 0.2561		2.87 [1.27, 6.46], 0.0110	
OR [95%-CI]; p-value	12.34 [1.54, 98.97], 0.0040		2.02 [0.62, 6.57], 0.2369		3.74 [1.44, 9.74], 0.0047	
RD [95%-CI]; p-value	0.28 [0.13, 0.42], 0.0002		0.13 [-0.08, 0.34], 0.2151		0.21 [0.08, 0.33], 0.0014	
Vist 13/ET:n/N1 (%)	19/51 (37.3)	3/28 (10.7)	18/40 (45.0)	5/26 (19.2)	37/91 (40.7)	8/54 (14.8)
RR [95%-CI]; p-value	3.48 [1.13, 10.73], 0.0302		2.34 [0.99, 5.52], 0.0524		2.74 [1.38, 5.45], 0.0039	
OR [95%-CI]; p-value	4.95 [1.31, 18.62], 0.0118		3.44 [1.08, 10.93], 0.0318		3.94 [1.67, 9.31], 0.0011	
RD [95%-CI]; p-value	0.27 [0.09, 0.44], 0.0030		0.26 [0.04, 0.47], 0.0195		0.26 [0.12, 0.40], 0.0003	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
EAP:n/N2 (%)	30/64 (46.9)	4/34 (11.8)	34/79 (43.0)	0/34 (0.0)	64/143 (44.8)	4/68 (5.9)
RR [95%-CI]; p-value	3.98 [1.53, 10.37], 0.0046		29.70 [1.87, 470.75], 0.0162		7.61 [2.89, 20.03], <0.0001	
OR [95%-CI]; p-value	6.62 [2.09, 20.96], 0.0005		51.38 [3.04, 868.37], <0.0001		12.96 [4.48, 37.51], <0.0001	
RD [95%-CI]; p-value	0.35 [0.19, 0.51], <0.0001		0.42 [0.30, 0.53], <0.0001		0.39 [0.29, 0.49], <0.0001	
Vist 13/ET:n/N2 (%)	30/64 (46.9)	3/34 (8.8)	40/79 (50.6)	2/34 (5.9)	70/143 (49.0)	5/68 (7.4)
RR [95%-CI]; p-value	5.31 [1.75, 16.14], 0.0032		8.61 [2.20, 33.61], 0.0020		6.66 [2.82, 15.73], <0.0001	
OR [95%-CI]; p-value	9.12 [2.53, 32.88], 0.0001		16.41 [3.68, 73.19], <0.0001		12.08 [4.59, 31.80], <0.0001	
RD [95%-CI]; p-value	0.38 [0.23, 0.54], <0.0001		0.45 [0.31, 0.58], <0.0001		0.42 [0.31, 0.52], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_1_1_1_m_pth30pct_age_pp.sas using SAS 9.4

Table 12.2.1.1.2.s1.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2862		0.0762		0.0436	
Vist 13/ET	0.3236		0.3911		0.1795	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
EAP:n/N1 (%)	37/51 (72.5)	9/28 (32.1)	30/40 (75.0)	11/26 (42.3)	67/91 (73.6)	20/54 (37.0)
RR [95%-CI]; p-value	2.26 [1.28, 3.97], 0.0047		1.77 [1.09, 2.87], 0.0202		1.99 [1.37, 2.87], 0.0003	
OR [95%-CI]; p-value	5.58 [2.05, 15.22], 0.0005		4.09 [1.42, 11.77], 0.0075		4.75 [2.30, 9.78], <0.0001	
RD [95%-CI]; p-value	0.40 [0.19, 0.62], 0.0002		0.33 [0.09, 0.56], 0.0059		0.37 [0.21, 0.52], <0.0001	
Vist 13/ET:n/N1 (%)	32/51 (62.7)	8/28 (28.6)	32/40 (80.0)	10/26 (38.5)	64/91 (70.3)	18/54 (33.3)
RR [95%-CI]; p-value	2.20 [1.18, 4.09], 0.0133		2.08 [1.25, 3.46], 0.0049		2.11 [1.41, 3.15], 0.0003	
OR [95%-CI]; p-value	4.21 [1.55, 11.41], 0.0037		6.40 [2.12, 19.35], 0.0006		4.74 [2.30, 9.77], <0.0001	
RD [95%-CI]; p-value	0.34 [0.13, 0.56], 0.0017		0.42 [0.19, 0.64], 0.0003		0.37 [0.21, 0.53], <0.0001	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
EAP:n/N2 (%)	48/64 (75.0)	7/34 (20.6)	55/79 (69.6)	6/34 (17.6)	103/143 (72.0)	13/68 (19.1)
RR [95%-CI]; p-value	3.64 [1.85, 7.16], 0.0002		3.95 [1.88, 8.27], 0.0003		3.77 [2.29, 6.21], <0.0001	
OR [95%-CI]; p-value	11.57 [4.23, 31.63], <0.0001		10.69 [3.92, 29.18], <0.0001		10.89 [5.38, 22.07], <0.0001	
RD [95%-CI]; p-value	0.54 [0.37, 0.72], <0.0001		0.52 [0.36, 0.68], <0.0001		0.53 [0.41, 0.65], <0.0001	
Vist 13/ET:n/N2 (%)	46/64 (71.9)	7/34 (20.6)	55/79 (69.6)	8/34 (23.5)	101/143 (70.6)	15/68 (22.1)
RR [95%-CI]; p-value	3.49 [1.77, 6.88], 0.0003		2.96 [1.59, 5.52], 0.0006		3.20 [2.02, 5.07], <0.0001	
OR [95%-CI]; p-value	9.86 [3.65, 26.63], <0.0001		7.45 [2.95, 18.81], <0.0001		8.50 [4.32, 16.72], <0.0001	
RD [95%-CI]; p-value	0.51 [0.34, 0.69], <0.0001		0.46 [0.29, 0.64], <0.0001		0.49 [0.36, 0.61], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_2_1_1_2_m_pth10pct_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4664		0.1545		0.1327	
Comparison Baseline vs. EAP	0.0567		0.1400		0.0146	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	18.7 (4.97)	19.7 (6.40)	17.4 (5.24)	18.1 (6.48)	18.2 (5.10)	18.9 (6.43)
Visit 13/ET						
n/N1	51/51	28/28	39/40	25/26	90/91	53/54
Mean (SD)	65.7 (25.28)	16.6 (6.42)	64.0 (25.45)	18.8 (6.98)	64.9 (25.23)	17.6 (6.71)
EAP						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	65.4 (25.79)	17.2 (6.09)	60.5 (21.76)	18.6 (6.77)	63.3 (24.10)	17.9 (6.40)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.9 (2.86)	-2.9 (3.86)	46.5 (3.26)	0.7 (4.08)	46.7 (2.16)	-1.1 (2.80)
95% CI	[41.19, 52.57]	[-10.60, 4.77]	[40.03, 53.07]	[-7.46, 8.85]	[42.43, 50.98]	[-6.68, 4.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.80		45.85		47.85	
95% CI	[40.23, 59.38]		[35.38, 56.32]		[40.85, 54.86]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.44		2.25		2.38	
95% CI	[1.85, 3.04]		[1.62, 2.89]		[1.94, 2.82]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.6 (2.94)	-2.2 (3.97)	43.0 (2.74)	0.7 (3.41)	44.7 (2.05)	-0.8 (2.64)
95% CI	[40.70, 52.41]	[-10.13, 5.69]	[37.50, 48.47]	[-6.14, 7.47]	[40.70, 48.78]	[-6.02, 4.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.77		42.32		45.54	
95% CI	[38.92, 58.63]		[33.57, 51.06]		[38.94, 52.15]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.32		2.42		2.37	
95% CI	[1.74, 2.91]		[1.78, 3.06]		[1.94, 2.80]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	20.7 (5.12)	18.9 (5.07)	20.7 (5.40)	20.2 (4.78)	20.7 (5.25)	19.5 (4.94)
Visit 13/ET						
n/N2	64/64	33/34	78/79	32/34	142/143	65/68
Mean (SD)	69.4 (22.72)	18.0 (6.26)	71.8 (20.70)	20.9 (6.83)	70.8 (21.59)	19.5 (6.66)
EAP						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	67.9 (19.59)	18.1 (6.48)	70.7 (19.71)	20.2 (6.37)	69.5 (19.64)	19.2 (6.47)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.2.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.6 (2.26)	-0.7 (3.16)	51.0 (1.99)	0.3 (3.11)	49.9 (1.50)	-0.3 (2.21)
95% CI	[44.12, 53.10]	[-7.00, 5.55]	[47.09, 54.97]	[-5.86, 6.46]	[46.93, 52.84]	[-4.69, 4.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.33		50.73		50.22	
95% CI	[41.57, 57.09]		[43.42, 58.04]		[44.95, 55.50]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.75		2.87		2.83	
95% CI	[2.18, 3.32]		[2.31, 3.42]		[2.43, 3.23]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.1 (1.91)	-0.5 (2.63)	50.0 (1.83)	0.0 (2.79)	48.6 (1.33)	-0.3 (1.92)
95% CI	[43.28, 50.87]	[-5.77, 4.69]	[46.36, 53.62]	[-5.52, 5.54]	[45.95, 51.19]	[-4.11, 3.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.61		49.98		48.90	
95% CI	[41.11, 54.12]		[43.36, 56.59]		[44.29, 53.51]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.14		3.06		3.12	
95% CI	[2.54, 3.74]		[2.50, 3.63]		[2.70, 3.53]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_2_1_m_25d_age_pp.sas using SAS 9.4

Table 12.3.1.1.s1.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4494		0.9103		0.4260	
Vist 13/ET	0.8864		0.6292		0.7158	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
EAP:n/N1 (%)	48/51 (94.1)	0/28 (0.0)	38/40 (95.0)	2/26 (7.7)	86/91 (94.5)	2/54 (3.7)
RR [95%-CI]; p-value	53.65 [3.44, 837.71], 0.0045		12.35 [3.26, 46.86], 0.0002		25.52 [6.54, 99.51], <0.0001	
OR [95%-CI]; p-value	896.00 [43.29, 18543.89], <0.0001		228.00 [30.08, 1728.20], <0.0001		447.20 [83.72, 2388.89], <0.0001	
RD [95%-CI]; p-value	0.92 [0.84, 1.00], <0.0001		0.87 [0.75, 1.00], <0.0001		0.91 [0.84, 0.98], <0.0001	
Vist 13/ET:n/N1 (%)	46/51 (90.2)	1/28 (3.6)	38/40 (95.0)	2/26 (7.7)	84/91 (92.3)	3/54 (5.6)
RR [95%-CI]; p-value	25.25 [3.68, 173.43], 0.0010		12.35 [3.26, 46.86], 0.0002		16.62 [5.52, 49.98], <0.0001	
OR [95%-CI]; p-value	248.40 [27.55, 2239.54], <0.0001		228.00 [30.08, 1728.20], <0.0001		204.00 [50.48, 824.40], <0.0001	
RD [95%-CI]; p-value	0.87 [0.76, 0.97], <0.0001		0.87 [0.75, 1.00], <0.0001		0.87 [0.79, 0.95], <0.0001	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
EAP:n/N2 (%)	62/64 (96.9)	2/34 (5.9)	78/79 (98.7)	3/34 (8.8)	140/143 (97.9)	5/68 (7.4)
RR [95%-CI]; p-value	16.47 [4.29, 63.23], <0.0001		11.19 [3.80, 32.98], <0.0001		13.31 [5.73, 30.97], <0.0001	
OR [95%-CI]; p-value	496.00 [66.73, 3686.50], <0.0001		806.00 [80.72, 8048.13], <0.0001		588.00 [136.29, 2536.75], <0.0001	
RD [95%-CI]; p-value	0.91 [0.82, 1.00], <0.0001		0.90 [0.80, 1.00], <0.0001		0.91 [0.84, 0.97], <0.0001	
Vist 13/ET:n/N2 (%)	58/64 (90.6)	1/34 (2.9)	77/79 (97.5)	4/34 (11.8)	135/143 (94.4)	5/68 (7.4)
RR [95%-CI]; p-value	30.81 [4.46, 212.82], 0.0005		8.28 [3.30, 20.81], <0.0001		12.84 [5.52, 29.88], <0.0001	
OR [95%-CI]; p-value	319.00 [36.80, 2765.29], <0.0001		288.75 [50.23, 1660.00], <0.0001		212.63 [66.88, 676.01], <0.0001	
RD [95%-CI]; p-value	0.88 [0.79, 0.97], <0.0001		0.86 [0.74, 0.97], <0.0001		0.87 [0.80, 0.94], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_3_1_1_m_25d30_age_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6730		0.3731		0.3415	
Comparison Baseline vs. EAP	0.1980		0.0455		0.0161	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	142.8 (54.55)	136.2 (43.20)	138.9 (60.31)	153.3 (68.23)	140.9 (57.29)	145.0 (57.69)
Visit 13/ET						
n/N1	58/59	28/29	58/59	30/31	116/118	58/60
Mean (SD)	110.7 (61.77)	142.9 (56.36)	97.9 (54.43)	160.4 (89.14)	104.3 (58.32)	152.0 (75.00)
EAP						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	104.4 (46.43)	148.6 (63.26)	103.4 (53.23)	161.5 (80.39)	103.9 (49.73)	155.3 (72.30)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.4 (5.71)	9.2 (8.23)	-42.9 (6.43)	8.5 (8.96)	-37.0 (4.29)	8.5 (6.07)
95% CI	[-42.78, -20.07]	[-7.15, 25.59]	[-55.64, -30.07]	[-9.34, 26.28]	[-45.45, -28.53]	[-3.45, 20.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.64		-51.33		-45.52	
95% CI	[-60.60, -20.68]		[-73.31, -29.34]		[-60.19, -30.86]	
p-value	0.0001		<0.0001		<0.0001	
Hedges' g	-0.95		-0.92		-0.94	
95% CI	[-1.42, -0.49]		[-1.38, -0.47]		[-1.27, -0.61]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-37.9 (4.87)	11.2 (6.95)	-36.5 (5.05)	10.0 (6.98)	-37.3 (3.50)	10.9 (4.91)
95% CI	[-47.54, -28.19]	[-2.57, 25.05]	[-46.54, -26.45]	[-3.88, 23.89]	[-44.22, -30.40]	[1.18, 20.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-49.11		-46.50		-48.19	
95% CI	[-65.98, -32.23]		[-63.68, -29.32]		[-60.10, -36.28]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.27		-1.07		-1.18	
95% CI	[-1.75, -0.79]		[-1.53, -0.61]		[-1.51, -0.85]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	146.1 (49.29)	137.6 (40.31)	146.8 (64.53)	154.5 (48.06)	146.5 (57.43)	145.5 (44.56)
Visit 13/ET						
n/N2	56/56	33/33	59/60	28/29	115/116	61/62
Mean (SD)	115.9 (62.12)	153.6 (74.82)	123.6 (111.26)	172.8 (59.48)	119.9 (90.42)	162.4 (68.35)
EAP						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	114.8 (56.08)	144.7 (69.53)	124.4 (95.08)	154.6 (43.60)	119.8 (78.52)	149.3 (58.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-29.6 (7.48)	15.1 (9.76)	-22.6 (8.48)	17.8 (12.32)	-26.7 (5.72)	17.5 (7.88)
95% CI	[-44.46, -14.72]	[-4.32, 34.46]	[-39.51, -5.78]	[-6.72, 42.27]	[-37.99, -15.40]	[1.91, 33.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-44.66		-40.42		-44.15	
95% CI	[-69.15, -20.18]		[-70.18, -10.66]		[-63.38, -24.93]	
p-value	0.0005		0.0084		<0.0001	
Hedges' g	-0.82		-0.63		-0.72	
95% CI	[-1.26, -0.37]		[-1.09, -0.17]		[-1.03, -0.40]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-31.0 (6.05)	6.6 (7.89)	-22.3 (6.89)	-0.1 (9.92)	-26.9 (4.59)	3.6 (6.29)
95% CI	[-43.01, -18.95]	[-9.08, 22.29]	[-35.99, -8.60]	[-19.86, 19.57]	[-35.92, -17.78]	[-8.80, 16.03]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.58		-22.16		-30.47	
95% CI	[-57.39, -17.78]		[-46.18, 1.87]		[-45.84, -15.09]	
p-value	0.0003		0.0702		0.0001	
Hedges' g	-0.84		-0.42		-0.62	
95% CI	[-1.29, -0.40]		[-0.86, 0.02]		[-0.93, -0.30]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_2_1_m_pth_sex_pp.sas using SAS 9.4

Table 12.2.1.1.1.s2.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2151		0.5568		0.1865	
Vist 13/ET	0.5820		0.9963		0.7167	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
EAP:n/N1 (%)	25/59 (42.4)	1/29 (3.4)	24/59 (40.7)	2/31 (6.5)	49/118 (41.5)	3/60 (5.0)
RR [95%-CI]; p-value	12.29 [1.75, 86.26], 0.0116		6.31 [1.59, 24.95], 0.0087		8.31 [2.70, 25.54], 0.0002	
OR [95%-CI]; p-value	20.59 [2.62, 161.60], 0.0002		9.94 [2.17, 45.65], 0.0007		13.49 [3.99, 45.58], <0.0001	
RD [95%-CI]; p-value	0.39 [0.25, 0.53], <0.0001		0.34 [0.19, 0.49], <0.0001		0.37 [0.26, 0.47], <0.0001	
Vist 13/ET:n/N1 (%)	24/59 (40.7)	2/29 (6.9)	32/59 (54.2)	4/31 (12.9)	56/118 (47.5)	6/60 (10.0)
RR [95%-CI]; p-value	5.90 [1.50, 23.27], 0.0113		4.20 [1.64, 10.81], 0.0029		4.75 [2.17, 10.38], <0.0001	
OR [95%-CI]; p-value	9.26 [2.01, 42.64], 0.0011		8.00 [2.49, 25.73], 0.0001		8.13 [3.25, 20.35], <0.0001	
RD [95%-CI]; p-value	0.34 [0.18, 0.49], <0.0001		0.41 [0.24, 0.59], <0.0001		0.37 [0.26, 0.49], <0.0001	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
EAP:n/N2 (%)	21/56 (37.5)	4/33 (12.1)	23/60 (38.3)	3/29 (10.3)	44/116 (37.9)	7/62 (11.3)
RR [95%-CI]; p-value	3.09 [1.16, 8.23], 0.0237		3.71 [1.21, 11.34], 0.0217		3.36 [1.61, 7.01], 0.0012	
OR [95%-CI]; p-value	4.35 [1.34, 14.12], 0.0101		5.39 [1.46, 19.84], 0.0065		4.80 [2.01, 11.48], 0.0002	
RD [95%-CI]; p-value	0.25 [0.09, 0.42], 0.0032		0.28 [0.11, 0.45], 0.0009		0.27 [0.15, 0.38], <0.0001	
Vist 13/ET:n/N2 (%)	25/56 (44.6)	4/33 (12.1)	26/60 (43.3)	3/29 (10.3)	51/116 (44.0)	7/62 (11.3)
RR [95%-CI]; p-value	3.68 [1.40, 9.66], 0.0080		4.19 [1.38, 12.71], 0.0114		3.89 [1.88, 8.06], 0.0002	
OR [95%-CI]; p-value	5.85 [1.81, 18.85], 0.0016		6.63 [1.81, 24.31], 0.0019		6.16 [2.59, 14.68], <0.0001	
RD [95%-CI]; p-value	0.33 [0.15, 0.50], 0.0002		0.33 [0.16, 0.50], 0.0001		0.33 [0.21, 0.45], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_1_1_1_m_pth30pct_sex_pp.sas using SAS 9.4

Table 12.2.1.1.2.s2.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2856		0.4932		0.7997	
Vist 13/ET	0.8161		0.7776		0.6923	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
EAP:n/N1 (%)	46/59 (78.0)	6/29 (20.7)	47/59 (79.7)	11/31 (35.5)	93/118 (78.8)	17/60 (28.3)
RR [95%-CI]; p-value	3.77 [1.82, 7.78], 0.0003		2.24 [1.37, 3.67], 0.0013		2.78 [1.84, 4.20], <0.0001	
OR [95%-CI]; p-value	13.56 [4.56, 40.31], <0.0001		7.12 [2.70, 18.81], <0.0001		9.41 [4.61, 19.22], <0.0001	
RD [95%-CI]; p-value	0.57 [0.39, 0.75], <0.0001		0.44 [0.24, 0.64], <0.0001		0.50 [0.37, 0.64], <0.0001	
Vist 13/ET:n/N1 (%)	43/59 (72.9)	8/29 (27.6)	44/59 (74.6)	10/31 (32.3)	87/118 (73.7)	18/60 (30.0)
RR [95%-CI]; p-value	2.64 [1.44, 4.86], 0.0018		2.31 [1.36, 3.93], 0.0020		2.46 [1.65, 3.67], <0.0001	
OR [95%-CI]; p-value	7.05 [2.60, 19.11], <0.0001		6.16 [2.37, 15.99], <0.0001		6.55 [3.29, 13.03], <0.0001	
RD [95%-CI]; p-value	0.45 [0.25, 0.65], <0.0001		0.42 [0.22, 0.62], <0.0001		0.44 [0.30, 0.58], <0.0001	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
EAP:n/N2 (%)	39/56 (69.6)	10/33 (30.3)	38/60 (63.3)	6/29 (20.7)	77/116 (66.4)	16/62 (25.8)
RR [95%-CI]; p-value	2.30 [1.33, 3.97], 0.0028		3.06 [1.46, 6.40], 0.0030		2.57 [1.65, 4.00], <0.0001	
OR [95%-CI]; p-value	5.28 [2.07, 13.45], 0.0003		6.62 [2.34, 18.75], 0.0002		5.68 [2.86, 11.28], <0.0001	
RD [95%-CI]; p-value	0.39 [0.20, 0.59], <0.0001		0.43 [0.24, 0.62], <0.0001		0.41 [0.27, 0.54], <0.0001	
Vist 13/ET:n/N2 (%)	35/56 (62.5)	7/33 (21.2)	43/60 (71.7)	8/29 (27.6)	78/116 (67.2)	15/62 (24.2)
RR [95%-CI]; p-value	2.95 [1.48, 5.86], 0.0021		2.60 [1.41, 4.78], 0.0022		2.78 [1.76, 4.40], <0.0001	
OR [95%-CI]; p-value	6.19 [2.29, 16.74], 0.0002		6.64 [2.47, 17.85], <0.0001		6.43 [3.20, 12.93], <0.0001	
RD [95%-CI]; p-value	0.41 [0.22, 0.60], <0.0001		0.44 [0.24, 0.64], <0.0001		0.43 [0.29, 0.57], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_2_1_1_2_m_pth10pct_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0876		0.2842		0.0462	
Comparison Baseline vs. EAP	0.2395		0.1711		0.0719	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	19.7 (5.08)	20.0 (5.38)	19.6 (5.31)	18.4 (4.94)	19.6 (5.18)	19.1 (5.17)
Visit 13/ET						
n/N1	59/59	28/29	58/59	29/31	117/118	57/60
Mean (SD)	74.5 (23.02)	17.9 (6.62)	73.0 (21.98)	18.3 (6.22)	73.8 (22.43)	18.1 (6.37)
EAP						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	73.3 (22.54)	18.5 (6.54)	70.4 (19.96)	18.1 (6.21)	71.9 (21.25)	18.3 (6.32)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	54.9 (2.40)	-2.2 (3.48)	53.5 (2.41)	-0.8 (3.41)	54.1 (1.71)	-1.3 (2.44)
95% CI	[50.14, 59.68]	[-9.09, 4.76]	[48.67, 58.26]	[-7.54, 6.03]	[50.73, 57.46]	[-6.09, 3.55]
Diff in LS-Mean [ER-Calcifediol - Placebo]	57.07		54.22		55.36	
95% CI	[48.66, 65.48]		[45.89, 62.54]		[49.48, 61.25]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.08		2.88		3.00	
95% CI	[2.44, 3.72]		[2.26, 3.49]		[2.56, 3.45]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	53.7 (2.35)	-1.5 (3.35)	50.9 (2.12)	-0.5 (2.93)	52.2 (1.58)	-0.9 (2.21)
95% CI	[48.99, 58.33]	[-8.17, 5.15]	[46.69, 55.11]	[-6.33, 5.30]	[49.12, 55.34]	[-5.28, 3.45]
Diff in LS-Mean [ER-Calcifediol - Placebo]	55.17		51.42		53.15	
95% CI	[47.04, 63.30]		[44.21, 58.62]		[47.78, 58.51]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.05		3.13		3.11	
95% CI	[2.42, 3.68]		[2.50, 3.76]		[2.66, 3.55]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	20.0 (5.21)	18.6 (5.93)	19.6 (5.82)	20.2 (6.24)	19.8 (5.52)	19.4 (6.08)
Visit 13/ET						
n/N2	56/56	33/33	59/60	28/29	115/116	61/62
Mean (SD)	60.6 (22.80)	16.9 (6.11)	65.5 (22.76)	21.7 (7.31)	63.1 (22.82)	19.1 (7.05)
EAP						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	60.0 (20.48)	17.1 (6.05)	64.2 (21.51)	21.0 (6.65)	62.2 (21.04)	18.9 (6.60)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.2.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	40.7 (2.41)	-1.8 (3.14)	46.0 (2.41)	1.1 (3.51)	43.3 (1.70)	-0.3 (2.34)
95% CI	[35.88, 45.45]	[-8.05, 4.44]	[41.17, 50.77]	[-5.84, 8.10]	[39.95, 46.65]	[-4.92, 4.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	42.47		44.84		43.60	
95% CI	[34.57, 50.37]		[36.37, 53.32]		[37.90, 49.30]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.35		2.42		2.40	
95% CI	[1.80, 2.89]		[1.85, 2.99]		[2.00, 2.79]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	40.1 (2.18)	-1.8 (2.84)	44.6 (2.22)	0.8 (3.20)	42.3 (1.55)	-0.4 (2.13)
95% CI	[35.74, 44.40]	[-7.45, 3.85]	[40.16, 49.00]	[-5.53, 7.19]	[39.22, 45.35]	[-4.61, 3.79]
Diff in LS-Mean [ER-Calcifediol - Placebo]	41.87		43.75		42.69	
95% CI	[34.72, 49.02]		[36.00, 51.50]		[37.49, 47.89]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.54		2.53		2.55	
95% CI	[1.97, 3.10]		[1.96, 3.11]		[2.15, 2.96]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_2_1_m_25d_sex_pp.sas using SAS 9.4

Table 12.3.1.1.s2.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3219		0.1693		0.7129	
Vist 13/ET	0.3350		0.1083		0.4745	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
EAP:n/N1 (%)	56/59 (94.9)	2/29 (6.9)	59/59 (100.0)	1/31 (3.2)	115/118 (97.5)	3/60 (5.0)
RR [95%-CI]; p-value	13.76 [3.61, 52.48], 0.0001		30.74 [4.47, 211.41], 0.0005		19.49 [6.47, 58.75], <0.0001	
OR [95%-CI]; p-value	252.00 [39.74, 1598.17], <0.0001		3540.00 [115.44, 108550.5], <0.0001		728.33 [142.49, 3722.88], <0.0001	
RD [95%-CI]; p-value	0.88 [0.77, 0.99], <0.0001		0.96 [0.89, 1.00], <0.0001		0.92 [0.86, 0.99], <0.0001	
Vist 13/ET:n/N1 (%)	54/59 (91.5)	2/29 (6.9)	58/59 (98.3)	1/31 (3.2)	112/118 (94.9)	3/60 (5.0)
RR [95%-CI]; p-value	13.27 [3.48, 50.66], 0.0002		30.47 [4.43, 209.62], 0.0005		18.98 [6.30, 57.24], <0.0001	
OR [95%-CI]; p-value	145.80 [26.54, 801.02], <0.0001		1740.00 [105.11, 28804.16], <0.0001		354.67 [85.55, 1470.41], <0.0001	
RD [95%-CI]; p-value	0.85 [0.73, 0.96], <0.0001		0.95 [0.88, 1.00], <0.0001		0.90 [0.83, 0.97], <0.0001	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
EAP:n/N2 (%)	54/56 (96.4)	0/33 (0.0)	57/60 (95.0)	4/29 (13.8)	111/116 (95.7)	4/62 (6.5)
RR [95%-CI]; p-value	64.61 [4.12, 1012.15], 0.0030		6.89 [2.77, 17.14], <0.0001		14.83 [5.74, 38.30], <0.0001	
OR [95%-CI]; p-value	1782.00 [77.98, 40724.28], <0.0001		118.75 [24.73, 570.24], <0.0001		321.90 [83.23, 1244.92], <0.0001	
RD [95%-CI]; p-value	0.95 [0.89, 1.00], <0.0001		0.81 [0.67, 0.95], <0.0001		0.89 [0.82, 0.96], <0.0001	
Vist 13/ET:n/N2 (%)	50/56 (89.3)	0/33 (0.0)	57/60 (95.0)	5/29 (17.2)	107/116 (92.2)	5/62 (8.1)
RR [95%-CI]; p-value	59.82 [3.81, 938.14], 0.0036		5.51 [2.48, 12.26], <0.0001		11.44 [4.93, 26.55], <0.0001	
OR [95%-CI]; p-value	550.00 [29.71, 10180.25], <0.0001		91.20 [20.17, 412.31], <0.0001		135.53 [43.37, 423.56], <0.0001	
RD [95%-CI]; p-value	0.88 [0.79, 0.97], <0.0001		0.78 [0.63, 0.93], <0.0001		0.84 [0.76, 0.93], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_3_1_1_m_25d30_sex_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6256		0.2292		0.2012	
Comparison Baseline vs. EAP	0.3354		0.0481		0.0266	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	145.1 (53.89)	129.2 (34.40)	150.5 (74.15)	170.1 (80.08)	147.8 (64.77)	147.4 (62.06)
Visit 13/ET						
n/N1	58/58	29/30	59/60	24/24	117/118	53/54
Mean (SD)	108.2 (64.24)	136.4 (46.72)	109.8 (89.05)	183.2 (87.74)	109.0 (77.41)	157.6 (71.64)
EAP						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	104.7 (49.64)	137.0 (53.37)	113.8 (74.32)	177.8 (85.40)	109.3 (63.30)	155.1 (71.72)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-35.1 (6.38)	7.4 (9.09)	-41.2 (7.22)	14.3 (11.35)	-38.7 (4.80)	12.1 (7.17)
95% CI	[-47.80, -22.41]	[-10.67, 25.47]	[-55.58, -26.85]	[-8.29, 36.89]	[-48.18, -29.22]	[-2.07, 26.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-42.51		-55.52		-50.78	
95% CI	[-64.78, -20.24]		[-82.36, -28.67]		[-67.81, -33.75]	
p-value	0.0003		<0.0001		<0.0001	
Hedges' g	-0.95		-0.96		-0.97	
95% CI	[-1.42, -0.49]		[-1.45, -0.47]		[-1.30, -0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-38.9 (4.91)	4.9 (6.85)	-37.3 (5.11)	9.3 (8.10)	-38.5 (3.54)	8.0 (5.27)
95% CI	[-48.66, -29.15]	[-8.75, 18.49]	[-47.49, -27.15]	[-6.80, 25.44]	[-45.50, -31.51]	[-2.38, 18.43]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-43.77		-46.64		-46.53	
95% CI	[-60.62, -26.93]		[-65.76, -27.53]		[-59.07, -33.99]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.21		-1.09		-1.16	
95% CI	[-1.69, -0.74]		[-1.59, -0.59]		[-1.51, -0.82]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	143.8 (50.17)	144.1 (46.34)	135.2 (46.82)	143.1 (36.38)	139.4 (48.48)	143.6 (41.05)
Visit 13/ET						
n/N2	56/57	32/32	58/59	34/36	114/116	66/68
Mean (SD)	118.5 (59.14)	159.9 (79.75)	112.0 (88.46)	154.5 (65.03)	115.2 (75.23)	157.1 (72.03)
EAP						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	114.3 (53.11)	155.5 (76.00)	114.1 (81.47)	145.1 (42.98)	114.2 (68.71)	150.0 (60.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-25.2 (6.84)	15.8 (9.05)	-23.2 (8.18)	10.8 (10.69)	-24.4 (5.37)	13.6 (7.06)
95% CI	[-38.76, -11.56]	[-2.17, 33.80]	[-39.47, -6.98]	[-10.47, 32.00]	[-34.99, -13.80]	[-0.31, 27.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.97		-33.98		-38.02	
95% CI	[-63.52, -18.43]		[-60.76, -7.21]		[-55.53, -20.50]	
p-value	0.0005		0.0135		<0.0001	
Hedges' g	-0.79		-0.56		-0.67	
95% CI	[-1.24, -0.35]		[-0.99, -0.13]		[-0.98, -0.36]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.5 (5.99)	11.4 (7.99)	-20.9 (6.85)	1.7 (8.78)	-25.3 (4.57)	6.8 (5.98)
95% CI	[-41.38, -17.57]	[-4.47, 27.31]	[-34.47, -7.26]	[-15.72, 19.15]	[-34.32, -16.30]	[-4.99, 18.60]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.90		-22.58		-32.11	
95% CI	[-60.75, -21.05]		[-44.73, -0.42]		[-46.96, -17.26]	
p-value	<0.0001		0.0459		<0.0001	
Hedges' g	-0.89		-0.44		-0.64	
95% CI	[-1.34, -0.44]		[-0.85, -0.02]		[-0.95, -0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_2_1_m_pth_wt_pp.sas using SAS 9.4

Table 12.2.1.1.1.s3.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3995		0.8276		0.4507	
Vist 13/ET	0.3406		0.9215		0.4431	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
EAP:n/N1 (%)	28/58 (48.3)	2/30 (6.7)	26/60 (43.3)	2/24 (8.3)	54/118 (45.8)	4/54 (7.4)
RR [95%-CI]; p-value	7.24 [1.85, 28.36], 0.0045		5.20 [1.34, 20.22], 0.0173		6.18 [2.36, 16.19], 0.0002	
OR [95%-CI]; p-value	13.07 [2.85, 59.99], <0.0001		8.41 [1.81, 39.04], 0.0021		10.55 [3.58, 31.09], <0.0001	
RD [95%-CI]; p-value	0.42 [0.26, 0.57], <0.0001		0.35 [0.18, 0.52], <0.0001		0.38 [0.27, 0.50], <0.0001	
Vist 13/ET:n/N1 (%)	27/58 (46.6)	2/30 (6.7)	32/60 (53.3)	3/24 (12.5)	59/118 (50.0)	5/54 (9.3)
RR [95%-CI]; p-value	6.98 [1.78, 27.40], 0.0053		4.27 [1.44, 12.62], 0.0087		5.40 [2.30, 12.69], 0.0001	
OR [95%-CI]; p-value	12.19 [2.65, 56.00], 0.0002		8.00 [2.15, 29.70], 0.0006		9.80 [3.65, 26.33], <0.0001	
RD [95%-CI]; p-value	0.40 [0.24, 0.56], <0.0001		0.41 [0.23, 0.59], <0.0001		0.41 [0.29, 0.53], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
EAP:n/N2 (%)	18/57 (31.6)	3/32 (9.4)	21/59 (35.6)	3/36 (8.3)	39/116 (33.6)	6/68 (8.8)
RR [95%-CI]; p-value	3.37 [1.07, 10.56], 0.0373		4.27 [1.37, 13.31], 0.0123		3.81 [1.70, 8.53], 0.0011	
OR [95%-CI]; p-value	4.46 [1.20, 16.59], 0.0179		6.08 [1.66, 22.23], 0.0030		5.23 [2.08, 13.16], 0.0002	
RD [95%-CI]; p-value	0.22 [0.06, 0.38], 0.0057		0.27 [0.12, 0.42], 0.0004		0.25 [0.14, 0.36], <0.0001	
Vist 13/ET:n/N2 (%)	22/57 (38.6)	4/32 (12.5)	26/59 (44.1)	4/36 (11.1)	48/116 (41.4)	8/68 (11.8)
RR [95%-CI]; p-value	3.09 [1.17, 8.17], 0.0232		3.97 [1.51, 10.44], 0.0053		3.52 [1.77, 6.98], 0.0003	
OR [95%-CI]; p-value	4.40 [1.36, 14.26], 0.0094		6.30 [1.98, 20.10], 0.0008		5.29 [2.32, 12.08], <0.0001	
RD [95%-CI]; p-value	0.26 [0.09, 0.43], 0.0027		0.33 [0.17, 0.49], <0.0001		0.30 [0.18, 0.41], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_1_1_1_m_pth30pct_wt_pp.sas using SAS 9.4

Table 12.2.1.1.2.s3.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.9797		0.5018		0.6262	
Vist 13/ET	0.8960		0.9872		0.9880	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
EAP:n/N1 (%)	44/58 (75.9)	8/30 (26.7)	45/60 (75.0)	6/24 (25.0)	89/118 (75.4)	14/54 (25.9)
RR [95%-CI]; p-value	2.84 [1.54, 5.24], 0.0008		3.00 [1.48, 6.09], 0.0024		2.91 [1.83, 4.62], <0.0001	
OR [95%-CI]; p-value	8.64 [3.15, 23.69], <0.0001		9.00 [3.02, 26.85], <0.0001		8.77 [4.19, 18.36], <0.0001	
RD [95%-CI]; p-value	0.49 [0.30, 0.68], <0.0001		0.50 [0.30, 0.70], <0.0001		0.49 [0.35, 0.64], <0.0001	
Vist 13/ET:n/N1 (%)	42/58 (72.4)	8/30 (26.7)	43/60 (71.7)	7/24 (29.2)	85/118 (72.0)	15/54 (27.8)
RR [95%-CI]; p-value	2.72 [1.47, 5.02], 0.0014		2.46 [1.29, 4.68], 0.0062		2.59 [1.66, 4.04], <0.0001	
OR [95%-CI]; p-value	7.22 [2.67, 19.49], <0.0001		6.14 [2.16, 17.45], 0.0003		6.70 [3.26, 13.74], <0.0001	
RD [95%-CI]; p-value	0.46 [0.26, 0.65], <0.0001		0.43 [0.21, 0.64], 0.0001		0.44 [0.30, 0.59], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
EAP:n/N2 (%)	41/57 (71.9)	8/32 (25.0)	40/59 (67.8)	11/36 (30.6)	81/116 (69.8)	19/68 (27.9)
RR [95%-CI]; p-value	2.88 [1.55, 5.36], 0.0009		2.22 [1.32, 3.74], 0.0028		2.50 [1.68, 3.73], <0.0001	
OR [95%-CI]; p-value	7.69 [2.87, 20.63], <0.0001		4.78 [1.95, 11.71], 0.0004		5.97 [3.08, 11.57], <0.0001	
RD [95%-CI]; p-value	0.47 [0.28, 0.66], <0.0001		0.37 [0.18, 0.56], 0.0001		0.42 [0.28, 0.55], <0.0001	
Vist 13/ET:n/N2 (%)	36/57 (63.2)	7/32 (21.9)	44/59 (74.6)	11/36 (30.6)	80/116 (69.0)	18/68 (26.5)
RR [95%-CI]; p-value	2.89 [1.46, 5.72], 0.0024		2.44 [1.46, 4.08], 0.0007		2.61 [1.72, 3.94], <0.0001	
OR [95%-CI]; p-value	6.12 [2.26, 16.58], 0.0002		6.67 [2.66, 16.73], <0.0001		6.17 [3.17, 12.03], <0.0001	
RD [95%-CI]; p-value	0.41 [0.22, 0.60], <0.0001		0.44 [0.25, 0.63], <0.0001		0.42 [0.29, 0.56], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_2_1_1_2_m_pth10pct_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3994		0.7073		0.3728	
Comparison Baseline vs. EAP	0.7559		0.7958		0.7010	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	19.7 (5.18)	20.7 (5.55)	20.4 (5.67)	19.4 (6.33)	20.1 (5.42)	20.2 (5.89)
Visit 13/ET						
n/N1	58/58	29/30	59/60	23/24	117/118	52/54
Mean (SD)	71.5 (23.67)	18.6 (5.94)	74.5 (22.28)	21.0 (7.03)	73.0 (22.93)	19.7 (6.50)
EAP						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	72.0 (24.59)	18.9 (6.01)	72.0 (21.39)	20.8 (7.36)	72.0 (22.92)	19.8 (6.64)

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	51.7 (2.52)	-2.2 (3.58)	54.2 (2.49)	1.1 (3.99)	52.9 (1.77)	-0.4 (2.67)
95% CI	[46.71, 56.75]	[-9.30, 4.92]	[49.25, 59.17]	[-6.82, 9.07]	[49.43, 56.42]	[-5.71, 4.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	53.92		53.09		53.36	
95% CI	[45.20, 62.65]		[43.71, 62.46]		[47.04, 59.69]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.81		2.73		2.80	
95% CI	[2.20, 3.41]		[2.10, 3.36]		[2.36, 3.24]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	52.3 (2.61)	-1.8 (3.63)	51.7 (2.33)	1.2 (3.69)	52.0 (1.74)	-0.2 (2.59)
95% CI	[47.10, 57.46]	[-8.98, 5.45]	[47.03, 56.30]	[-6.12, 8.56]	[48.52, 55.39]	[-5.34, 4.88]
Diff in LS-Mean [ER-Calcifediol - Placebo]	54.04		50.44		52.18	
95% CI	[45.15, 62.94]		[41.75, 59.13]		[46.02, 58.35]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.72		2.77		2.78	
95% CI	[2.13, 3.32]		[2.15, 3.40]		[2.34, 3.21]	

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	20.0 (5.12)	17.9 (5.51)	18.8 (5.36)	19.2 (5.21)	19.4 (5.25)	18.5 (5.35)
Visit 13/ET						
n/N2	57/57	32/32	58/59	34/36	115/116	66/68
Mean (SD)	64.0 (23.66)	16.3 (6.54)	63.9 (21.82)	19.3 (6.87)	63.9 (22.65)	17.8 (6.83)
EAP						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	61.5 (18.88)	16.6 (6.38)	62.5 (19.40)	18.7 (5.89)	62.0 (19.07)	17.7 (6.17)

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.2.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	43.9 (2.47)	-1.4 (3.31)	44.9 (2.30)	-0.2 (3.01)	44.5 (1.68)	-0.9 (2.22)
95% CI	[39.00, 48.83]	[-7.94, 5.24]	[40.33, 49.48]	[-6.16, 5.80]	[41.20, 47.83]	[-5.32, 3.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	45.27		45.09		45.46	
95% CI	[36.98, 53.56]		[37.55, 52.62]		[39.95, 50.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.45		2.57		2.53	
95% CI	[1.89, 3.01]		[2.01, 3.13]		[2.13, 2.93]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	41.6 (1.99)	-1.4 (2.67)	43.6 (1.98)	-0.5 (2.54)	42.6 (1.40)	-1.0 (1.83)
95% CI	[37.65, 45.58]	[-6.72, 3.91]	[39.69, 47.56]	[-5.50, 4.57]	[39.88, 45.40]	[-4.59, 2.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	43.02		44.09		43.62	
95% CI	[36.33, 49.71]		[37.69, 50.48]		[39.06, 48.17]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.86		2.89		2.89	
95% CI	[2.26, 3.46]		[2.31, 3.47]		[2.47, 3.31]	

Abbreviations: 1,25 D: 1,25-dihydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_2_1_m_25d_wt_pp.sas using SAS 9.4

Table 12.3.1.1.s3.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.9165		0.0961		0.1421	
Vist 13/ET	0.3548		0.6007		0.3018	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
EAP:n/N1 (%)	53/58 (91.4)	1/30 (3.3)	58/60 (96.7)	4/24 (16.7)	111/118 (94.1)	5/54 (9.3)
RR [95%-CI]; p-value	27.41 [3.98, 188.61], 0.0008		5.80 [2.37, 14.21], 0.0001		10.16 [4.40, 23.44], <0.0001	
OR [95%-CI]; p-value	307.40 [34.26, 2758.36], <0.0001		145.00 [24.65, 852.84], <0.0001		155.40 [47.00, 513.81], <0.0001	
RD [95%-CI]; p-value	0.88 [0.78, 0.98], <0.0001		0.80 [0.64, 0.96], <0.0001		0.85 [0.76, 0.94], <0.0001	
Vist 13/ET:n/N1 (%)	53/58 (91.4)	2/30 (6.7)	58/60 (96.7)	3/24 (12.5)	111/118 (94.1)	5/54 (9.3)
RR [95%-CI]; p-value	13.71 [3.58, 52.41], 0.0001		7.73 [2.68, 22.31], 0.0002		10.16 [4.40, 23.44], <0.0001	
OR [95%-CI]; p-value	148.40 [27.04, 814.41], <0.0001		203.00 [31.68, 1300.79], <0.0001		155.40 [47.00, 513.81], <0.0001	
RD [95%-CI]; p-value	0.85 [0.73, 0.96], <0.0001		0.84 [0.70, 0.98], <0.0001		0.85 [0.76, 0.94], <0.0001	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
EAP:n/N2 (%)	57/57 (100.0)	1/32 (3.1)	58/59 (98.3)	1/36 (2.8)	115/116 (99.1)	2/68 (2.9)
RR [95%-CI]; p-value	31.72 [4.61, 218.38], 0.0004		35.39 [5.12, 244.51], 0.0003		33.71 [8.60, 132.05], <0.0001	
OR [95%-CI]; p-value	3534.00 [115.28, 108337.3], <0.0001		2030.00 [123.03, 33495.46], <0.0001		3795.00 [337.64, 42655.08], <0.0001	
RD [95%-CI]; p-value	0.96 [0.90, 1.00], <0.0001		0.96 [0.89, 1.00], <0.0001		0.96 [0.92, 1.00], <0.0001	
Vist 13/ET:n/N2 (%)	51/57 (89.5)	0/32 (0.0)	57/59 (96.6)	3/36 (8.3)	108/116 (93.1)	3/68 (4.4)
RR [95%-CI]; p-value	58.16 [3.71, 911.42], 0.0038		11.59 [3.92, 34.29], <0.0001		21.10 [6.97, 63.87], <0.0001	
OR [95%-CI]; p-value	544.00 [29.38, 10072.87], <0.0001		313.50 [49.80, 1973.65], <0.0001		292.50 [74.92, 1142.04], <0.0001	
RD [95%-CI]; p-value	0.88 [0.79, 0.97], <0.0001		0.88 [0.78, 0.98], <0.0001		0.89 [0.82, 0.95], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_3_1_1_m_25d30_wt_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7713		0.3054		0.4244	
Comparison Baseline vs. EAP	0.7884		0.5664		0.9521	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	137.4 (46.21)	129.5 (37.91)	138.8 (56.08)	143.6 (41.14)	138.2 (51.81)	136.4 (39.90)
Visit 13/ET						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	105.8 (56.48)	141.7 (57.85)	101.4 (79.96)	157.8 (63.46)	103.3 (70.42)	149.5 (60.81)
EAP						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	101.8 (49.20)	133.3 (50.35)	106.2 (75.16)	148.2 (45.88)	104.3 (64.89)	140.6 (48.50)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.0 (5.74)	11.1 (7.24)	-37.6 (6.63)	14.7 (9.67)	-34.4 (4.49)	13.0 (6.06)
95% CI	[-42.34, -19.56]	[-3.27, 25.44]	[-50.69, -24.45]	[-4.48, 33.81]	[-43.25, -25.57]	[1.09, 24.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-42.03		-52.23		-47.44	
95% CI	[-60.40, -23.67]		[-75.45, -29.02]		[-62.30, -32.58]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.92		-0.85		-0.88	
95% CI	[-1.33, -0.52]		[-1.24, -0.46]		[-1.16, -0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.9 (4.57)	2.7 (5.76)	-32.7 (5.39)	5.0 (7.87)	-34.0 (3.63)	4.1 (4.90)
95% CI	[-43.98, -25.85]	[-8.69, 14.16]	[-43.37, -22.03]	[-10.57, 20.58]	[-41.13, -26.83]	[-5.57, 13.74]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-37.65		-37.71		-38.07	
95% CI	[-52.26, -23.04]		[-56.60, -18.81]		[-50.08, -26.05]	
p-value	<0.0001		0.0001		<0.0001	
Hedges' g	-1.03		-0.75		-0.86	
95% CI	[-1.45, -0.62]		[-1.14, -0.36]		[-1.14, -0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	153.6 (57.58)	151.4 (44.81)	152.4 (74.83)	173.1 (80.02)	153.1 (64.94)	162.3 (65.00)
Visit 13/ET						
n/N2	49/50	20/21	34/36	19/21	83/86	39/42
Mean (SD)	123.2 (67.38)	163.2 (81.62)	134.0 (103.90)	184.1 (96.12)	127.6 (83.85)	173.4 (88.43)
EAP						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	119.4 (52.95)	172.3 (84.99)	131.8 (81.26)	176.7 (88.53)	124.6 (66.13)	174.5 (85.74)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.1 (7.95)	15.4 (12.45)	-19.3 (9.71)	7.1 (13.02)	-25.2 (6.27)	12.2 (9.01)
95% CI	[-46.00, -14.26]	[-9.41, 40.30]	[-38.84, 0.16]	[-19.07, 33.24]	[-37.60, -12.76]	[-5.65, 30.02]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.58		-26.43		-37.36	
95% CI	[-75.08, -16.07]		[-59.19, 6.33]		[-59.11, -15.61]	
p-value	0.0030		0.1115		0.0009	
Hedges' g	-0.83		-0.49		-0.68	
95% CI	[-1.36, -0.29]		[-1.05, 0.07]		[-1.07, -0.30]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-34.0 (6.71)	20.6 (10.36)	-21.0 (7.19)	4.3 (9.44)	-27.7 (4.99)	13.0 (7.05)
95% CI	[-47.42, -20.62]	[-0.05, 41.31]	[-35.45, -6.60]	[-14.60, 23.25]	[-37.59, -17.85]	[-0.99, 26.91]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-54.65		-25.35		-40.68	
95% CI	[-79.29, -30.01]		[-49.24, -1.46]		[-57.79, -23.57]	
p-value	<0.0001		0.0380		<0.0001	
Hedges' g	-1.13		-0.56		-0.88	
95% CI	[-1.66, -0.59]		[-1.10, -0.02]		[-1.26, -0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_2_1_m_pth_race_pp.sas using SAS 9.4

Table 12.2.1.1.1.s4.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4678		0.0785		0.4946	
Vist 13/ET	0.3189		0.7022		0.6023	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
EAP:n/N1 (%)	25/65 (38.5)	4/41 (9.8)	38/83 (45.8)	2/39 (5.1)	63/148 (42.6)	6/80 (7.5)
RR [95%-CI]; p-value	3.94 [1.48, 10.51], 0.0061		8.93 [2.27, 35.14], 0.0017		5.68 [2.57, 12.53], <0.0001	
OR [95%-CI]; p-value	5.78 [1.84, 18.19], 0.0012		15.62 [3.53, 69.11], <0.0001		9.14 [3.74, 22.34], <0.0001	
RD [95%-CI]; p-value	0.29 [0.14, 0.44], 0.0002		0.41 [0.28, 0.53], <0.0001		0.35 [0.25, 0.45], <0.0001	
Vist 13/ET:n/N1 (%)	26/65 (40.0)	5/41 (12.2)	47/83 (56.6)	5/39 (12.8)	73/148 (49.3)	10/80 (12.5)
RR [95%-CI]; p-value	3.28 [1.37, 7.86], 0.0077		4.42 [1.91, 10.23], 0.0005		3.95 [2.16, 7.21], <0.0001	
OR [95%-CI]; p-value	4.80 [1.66, 13.84], 0.0022		8.88 [3.16, 24.97], <0.0001		6.81 [3.26, 14.23], <0.0001	
RD [95%-CI]; p-value	0.28 [0.12, 0.43], 0.0005		0.44 [0.29, 0.59], <0.0001		0.37 [0.26, 0.48], <0.0001	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
EAP:n/N2 (%)	21/50 (42.0)	1/21 (4.8)	9/36 (25.0)	3/21 (14.3)	30/86 (34.9)	4/42 (9.5)
RR [95%-CI]; p-value	8.82 [1.27, 61.39], 0.0279		1.75 [0.53, 5.76], 0.3570		3.66 [1.38, 9.72], 0.0091	
OR [95%-CI]; p-value	14.48 [1.80, 116.56], 0.0020		2.00 [0.48, 8.41], 0.3385		5.09 [1.66, 15.62], 0.0023	
RD [95%-CI]; p-value	0.37 [0.21, 0.54], <0.0001		0.11 [-0.10, 0.31], 0.3078		0.25 [0.12, 0.39], 0.0002	
Vist 13/ET:n/N2 (%)	23/50 (46.0)	1/21 (4.8)	11/36 (30.6)	2/21 (9.5)	34/86 (39.5)	3/42 (7.1)
RR [95%-CI]; p-value	9.66 [1.39, 66.96], 0.0217		3.21 [0.79, 13.10], 0.1045		5.53 [1.80, 16.99], 0.0028	
OR [95%-CI]; p-value	17.04 [2.12, 136.91], 0.0008		4.18 [0.83, 21.13], 0.0679		8.50 [2.43, 29.71], 0.0001	
RD [95%-CI]; p-value	0.41 [0.25, 0.58], <0.0001		0.21 [0.01, 0.41], 0.0354		0.32 [0.19, 0.45], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_1_1_1_m_pth30pct_race_pp.sas using SAS 9.4

Table 12.2.1.1.2.s4.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.5223		0.1304		0.6001	
Vist 13/ET	0.5815		0.5979		0.9746	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
EAP:n/N1 (%)	50/65 (76.9)	12/41 (29.3)	66/83 (79.5)	10/39 (25.6)	116/148 (78.4)	22/80 (27.5)
RR [95%-CI]; p-value	2.63 [1.60, 4.31], 0.0001		3.10 [1.80, 5.35], <0.0001		2.85 [1.98, 4.11], <0.0001	
OR [95%-CI]; p-value	8.06 [3.32, 19.54], <0.0001		11.26 [4.60, 27.55], <0.0001		9.56 [5.10, 17.90], <0.0001	
RD [95%-CI]; p-value	0.48 [0.30, 0.65], <0.0001		0.54 [0.38, 0.70], <0.0001		0.51 [0.39, 0.63], <0.0001	
Vist 13/ET:n/N1 (%)	45/65 (69.2)	11/41 (26.8)	66/83 (79.5)	12/39 (30.8)	111/148 (75.0)	23/80 (28.8)
RR [95%-CI]; p-value	2.58 [1.52, 4.39], 0.0005		2.58 [1.59, 4.19], 0.0001		2.61 [1.82, 3.73], <0.0001	
OR [95%-CI]; p-value	6.14 [2.57, 14.63], <0.0001		8.74 [3.68, 20.73], <0.0001		7.43 [4.04, 13.69], <0.0001	
RD [95%-CI]; p-value	0.42 [0.25, 0.60], <0.0001		0.49 [0.32, 0.66], <0.0001		0.46 [0.34, 0.58], <0.0001	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
EAP:n/N2 (%)	35/50 (70.0)	4/21 (19.0)	19/36 (52.8)	7/21 (33.3)	54/86 (62.8)	11/42 (26.2)
RR [95%-CI]; p-value	3.68 [1.49, 9.04], 0.0046		1.58 [0.80, 3.12], 0.1848		2.40 [1.41, 4.09], 0.0013	
OR [95%-CI]; p-value	9.92 [2.85, 34.47], <0.0001		2.24 [0.73, 6.84], 0.1551		4.76 [2.10, 10.74], 0.0001	
RD [95%-CI]; p-value	0.51 [0.30, 0.72], <0.0001		0.19 [-0.06, 0.45], 0.1417		0.37 [0.20, 0.53], <0.0001	
Vist 13/ET:n/N2 (%)	33/50 (66.0)	4/21 (19.0)	21/36 (58.3)	6/21 (28.6)	54/86 (62.8)	10/42 (23.8)
RR [95%-CI]; p-value	3.47 [1.40, 8.56], 0.0070		2.04 [0.98, 4.24], 0.0555		2.64 [1.50, 4.64], 0.0008	
OR [95%-CI]; p-value	8.25 [2.40, 28.41], 0.0003		3.50 [1.10, 11.12], 0.0299		5.40 [2.35, 12.43], <0.0001	
RD [95%-CI]; p-value	0.47 [0.26, 0.68], <0.0001		0.30 [0.05, 0.55], 0.0204		0.39 [0.23, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_2_1_1_2_m_pth10pct_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0709		0.7026		0.2632	
Comparison Baseline vs. EAP	0.0488		0.8874		0.0993	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	20.7 (4.64)	19.9 (5.81)	20.3 (5.25)	20.2 (5.47)	20.5 (4.98)	20.0 (5.61)
Visit 13/ET						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	69.7 (21.49)	17.7 (6.37)	70.3 (23.56)	20.6 (7.05)	70.0 (22.60)	19.1 (6.84)
EAP						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	67.8 (19.76)	17.9 (6.27)	69.0 (21.48)	20.5 (6.71)	68.5 (20.68)	19.1 (6.58)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.1 (2.12)	-2.4 (2.68)	50.1 (2.12)	0.5 (3.09)	49.5 (1.51)	-0.9 (2.05)
95% CI	[44.85, 53.27]	[-7.71, 2.90]	[45.87, 54.25]	[-5.64, 6.59]	[46.55, 52.52]	[-4.95, 3.11]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.47		49.58		50.46	
95% CI	[44.68, 58.25]		[42.17, 57.00]		[45.44, 55.47]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.97		2.57		2.76	
95% CI	[2.41, 3.52]		[2.07, 3.06]		[2.39, 3.13]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.2 (1.95)	-2.2 (2.46)	48.8 (1.88)	0.3 (2.75)	48.0 (1.37)	-0.9 (1.85)
95% CI	[43.36, 51.11]	[-7.10, 2.66]	[45.05, 52.51]	[-5.12, 5.76]	[45.27, 50.66]	[-4.53, 2.76]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.45		48.46		48.85	
95% CI	[43.21, 55.69]		[41.87, 55.06]		[44.31, 53.38]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.09		2.82		2.96	
95% CI	[2.52, 3.66]		[2.30, 3.33]		[2.58, 3.35]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	18.7 (5.55)	18.0 (5.29)	18.2 (6.02)	17.6 (5.69)	18.5 (5.72)	17.8 (5.43)
Visit 13/ET						
n/N2	50/50	20/21	34/36	18/21	84/86	38/42
Mean (SD)	65.3 (26.65)	16.8 (6.32)	66.6 (20.12)	18.6 (6.60)	65.8 (24.09)	17.6 (6.43)
EAP						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	65.5 (25.74)	17.4 (6.42)	63.2 (19.17)	17.7 (5.95)	64.6 (23.12)	17.6 (6.12)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.2.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.5 (3.05)	-1.0 (4.83)	48.4 (2.90)	0.3 (3.99)	47.5 (2.22)	-0.6 (3.24)
95% CI	[40.42, 52.61]	[-10.61, 8.67]	[42.53, 54.19]	[-7.73, 8.29]	[43.14, 51.93]	[-6.99, 5.86]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.49		48.08		48.10	
95% CI	[36.07, 58.91]		[38.17, 57.99]		[40.32, 55.88]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.19		2.74		2.41	
95% CI	[1.56, 2.82]		[1.97, 3.52]		[1.93, 2.90]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.7 (2.97)	-0.4 (4.58)	45.2 (2.63)	-0.1 (3.44)	46.0 (2.07)	-0.3 (2.93)
95% CI	[40.81, 52.65]	[-9.57, 8.72]	[39.95, 50.48]	[-7.04, 6.75]	[41.86, 50.07]	[-6.12, 5.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.15		45.36		46.29	
95% CI	[36.25, 58.05]		[36.68, 54.04]		[39.18, 53.39]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.24		2.75		2.45	
95% CI	[1.62, 2.87]		[2.02, 3.48]		[1.98, 2.93]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_2_1_m_25d_race_pp.sas using SAS 9.4

Table 12.3.1.1.s4.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.5958		0.2547		0.3060	
Vist 13/ET	0.6753		0.3890		0.2495	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
EAP:n/N1 (%)	64/65 (98.5)	1/41 (2.4)	82/83 (98.8)	5/39 (12.8)	146/148 (98.6)	6/80 (7.5)
RR [95%-CI]; p-value	40.37 [5.82, 279.84], 0.0002		7.71 [3.40, 17.47], <0.0001		13.15 [6.09, 28.40], <0.0001	
OR [95%-CI]; p-value	2560.00 [155.70, 42090.61], <0.0001		557.60 [62.78, 4952.16], <0.0001		900.33 [177.36, 4570.26], <0.0001	
RD [95%-CI]; p-value	0.96 [0.90, 1.00], <0.0001		0.86 [0.75, 0.97], <0.0001		0.91 [0.85, 0.97], <0.0001	
Vist 13/ET:n/N1 (%)	61/65 (93.8)	2/41 (4.9)	82/83 (98.8)	5/39 (12.8)	143/148 (96.6)	7/80 (8.8)
RR [95%-CI]; p-value	19.24 [4.97, 74.44], <0.0001		7.71 [3.40, 17.47], <0.0001		11.04 [5.44, 22.42], <0.0001	
OR [95%-CI]; p-value	297.38 [51.97, 1701.54], <0.0001		557.60 [62.78, 4952.16], <0.0001		298.26 [91.49, 972.35], <0.0001	
RD [95%-CI]; p-value	0.89 [0.80, 0.98], <0.0001		0.86 [0.75, 0.97], <0.0001		0.88 [0.81, 0.95], <0.0001	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
EAP:n/N2 (%)	46/50 (92.0)	1/21 (4.8)	34/36 (94.4)	0/21 (0.0)	80/86 (93.0)	1/42 (2.4)
RR [95%-CI]; p-value	19.32 [2.85, 131.05], 0.0024		40.61 [2.62, 629.28], 0.0081		39.07 [5.63, 271.16], 0.0002	
OR [95%-CI]; p-value	230.00 [24.16, 2189.41], <0.0001		714.00 [30.71, 16601.35], <0.0001		546.67 [63.66, 4694.05], <0.0001	
RD [95%-CI]; p-value	0.87 [0.75, 0.99], <0.0001		0.92 [0.82, 1.00], <0.0001		0.91 [0.84, 0.98], <0.0001	
Vist 13/ET:n/N2 (%)	43/50 (86.0)	0/21 (0.0)	33/36 (91.7)	1/21 (4.8)	76/86 (88.4)	1/42 (2.4)
RR [95%-CI]; p-value	36.98 [2.38, 573.67], 0.0099		19.25 [2.84, 130.68], 0.0025		37.12 [5.34, 257.77], 0.0003	
OR [95%-CI]; p-value	258.00 [13.97, 4765.29], <0.0001		220.00 [21.40, 2261.89], <0.0001		311.60 [38.52, 2520.31], <0.0001	
RD [95%-CI]; p-value	0.84 [0.72, 0.95], <0.0001		0.87 [0.74, 1.00], <0.0001		0.86 [0.78, 0.94], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_3_1_1_m_25d30_race_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2237		0.8262		0.5806	
Comparison Baseline vs. EAP	0.0797		0.8073		0.4432	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	124.4 (39.82)	128.1 (33.64)	127.2 (34.87)	146.5 (59.64)	125.9 (37.16)	136.7 (48.08)
Visit 13/ET						
n/N1	57/58	33/33	63/65	27/29	120/123	60/62
Mean (SD)	99.3 (43.38)	137.8 (69.57)	94.8 (37.18)	142.4 (77.08)	97.0 (40.14)	139.9 (72.45)
EAP						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	95.8 (38.63)	133.4 (65.28)	98.7 (35.50)	140.3 (63.89)	97.3 (36.89)	136.6 (64.20)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-25.1 (6.44)	10.7 (8.47)	-33.0 (4.29)	-2.7 (6.60)	-29.2 (3.85)	4.5 (5.49)
95% CI	[-37.94, -12.35]	[-6.16, 27.49]	[-41.48, -24.44]	[-15.77, 10.47]	[-36.83, -21.63]	[-6.34, 15.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.81		-30.31		-33.73	
95% CI	[-56.97, -14.66]		[-46.08, -14.53]		[-47.01, -20.44]	
p-value	0.0011		0.0003		<0.0001	
Hedges' g	-0.68		-0.83		-0.75	
95% CI	[-1.12, -0.25]		[-1.29, -0.36]		[-1.07, -0.43]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-29.0 (5.57)	6.0 (7.38)	-29.5 (3.47)	-4.0 (5.23)	-29.4 (3.23)	1.3 (4.57)
95% CI	[-40.07, -17.94]	[-8.69, 20.65]	[-36.37, -22.59]	[-14.38, 6.42]	[-35.75, -22.98]	[-7.76, 10.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-34.98		-25.50		-30.63	
95% CI	[-53.37, -16.60]		[-38.08, -12.92]		[-41.72, -19.53]	
p-value	0.0003		0.0001		<0.0001	
Hedges' g	-0.77		-0.78		-0.78	
95% CI	[-1.21, -0.33]		[-1.23, -0.33]		[-1.09, -0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	164.8 (54.99)	147.0 (47.27)	161.8 (80.73)	160.9 (58.21)	163.3 (68.43)	154.2 (53.22)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	127.2 (73.56)	161.5 (61.85)	129.6 (121.72)	187.3 (69.45)	128.4 (99.47)	175.1 (66.66)
EAP						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	123.3 (58.90)	161.5 (65.02)	132.4 (106.10)	174.9 (62.08)	127.7 (84.92)	168.4 (63.34)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-37.1 (6.77)	16.9 (9.72)	-32.2 (10.55)	26.4 (13.92)	-34.8 (6.21)	21.9 (8.54)
95% CI	[-50.59, -23.64]	[-2.48, 36.21]	[-53.18, -11.23]	[-1.31, 54.06]	[-47.05, -22.52]	[5.02, 38.74]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-53.98		-58.58		-56.67	
95% CI	[-77.74, -30.21]		[-93.32, -23.84]		[-77.55, -35.78]	
p-value	<0.0001		0.0012		<0.0001	
Hedges' g	-1.08		-0.75		-0.88	
95% CI	[-1.56, -0.61]		[-1.21, -0.30]		[-1.21, -0.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-40.7 (5.39)	13.0 (7.59)	-29.4 (8.41)	14.0 (11.10)	-35.2 (4.95)	13.8 (6.74)
95% CI	[-51.38, -29.94]	[-2.07, 28.12]	[-46.11, -12.66]	[-8.09, 36.05]	[-44.93, -25.39]	[0.48, 27.08]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-53.69		-43.37		-48.94	
95% CI	[-72.31, -35.06]		[-71.06, -15.68]		[-65.47, -32.42]	
p-value	<0.0001		0.0025		<0.0001	
Hedges' g	-1.36		-0.70		-0.95	
95% CI	[-1.85, -0.87]		[-1.15, -0.25]		[-1.28, -0.62]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_2_1_m_pth_ckd_pp.sas using SAS 9.4

Table 12.2.1.1.1.s5.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.2858		0.5581		0.2374	
Vist 13/ET	0.1803		0.4125		0.1276	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
EAP:n/N1 (%)	24/58 (41.4)	4/33 (12.1)	25/65 (38.5)	3/29 (10.3)	49/123 (39.8)	7/62 (11.3)
RR [95%-CI]; p-value	3.41 [1.30, 8.99], 0.0130		3.72 [1.22, 11.33], 0.0209		3.53 [1.70, 7.33], 0.0007	
OR [95%-CI]; p-value	5.12 [1.59, 16.47], 0.0036		5.42 [1.48, 19.78], 0.0059		5.20 [2.19, 12.36], <0.0001	
RD [95%-CI]; p-value	0.29 [0.12, 0.46], 0.0007		0.28 [0.12, 0.44], 0.0007		0.29 [0.17, 0.40], <0.0001	
Vist 13/ET:n/N1 (%)	25/58 (43.1)	5/33 (15.2)	28/65 (43.1)	4/29 (13.8)	53/123 (43.1)	9/62 (14.5)
RR [95%-CI]; p-value	2.84 [1.20, 6.72], 0.0172		3.12 [1.21, 8.09], 0.0190		2.97 [1.57, 5.61], 0.0008	
OR [95%-CI]; p-value	4.24 [1.43, 12.55], 0.0064		4.73 [1.48, 15.15], 0.0057		4.46 [2.02, 9.84], 0.0001	
RD [95%-CI]; p-value	0.28 [0.10, 0.46], 0.0019		0.29 [0.12, 0.47], 0.0010		0.29 [0.16, 0.41], <0.0001	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
EAP:n/N2 (%)	22/57 (38.6)	1/29 (3.4)	22/54 (40.7)	2/31 (6.5)	44/111 (39.6)	3/60 (5.0)
RR [95%-CI]; p-value	11.19 [1.59, 78.95], 0.0154		6.31 [1.59, 25.06], 0.0088		7.93 [2.57, 24.46], 0.0003	
OR [95%-CI]; p-value	17.60 [2.23, 138.74], 0.0005		9.97 [2.15, 46.14], 0.0007		12.48 [3.68, 42.34], <0.0001	
RD [95%-CI]; p-value	0.35 [0.21, 0.49], <0.0001		0.34 [0.19, 0.50], <0.0001		0.35 [0.24, 0.45], <0.0001	
Vist 13/ET:n/N2 (%)	24/57 (42.1)	1/29 (3.4)	30/54 (55.6)	3/31 (9.7)	54/111 (48.6)	4/60 (6.7)
RR [95%-CI]; p-value	12.21 [1.74, 85.81], 0.0119		5.74 [1.91, 17.27], 0.0019		7.30 [2.78, 19.17], <0.0001	
OR [95%-CI]; p-value	20.36 [2.59, 160.22], 0.0002		11.67 [3.16, 43.07], <0.0001		13.26 [4.50, 39.08], <0.0001	
RD [95%-CI]; p-value	0.39 [0.24, 0.53], <0.0001		0.46 [0.29, 0.63], <0.0001		0.42 [0.31, 0.53], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_1_1_1_m_pth30pct_ckd_pp.sas using SAS 9.4

Table 12.2.1.1.2.s5.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4172		0.4241		0.2575	
Vist 13/ET	0.2466		0.6740		0.2817	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
EAP:n/N1 (%)	43/58 (74.1)	10/33 (30.3)	48/65 (73.8)	10/29 (34.5)	91/123 (74.0)	20/62 (32.3)
RR [95%-CI]; p-value	2.45 [1.43, 4.20], 0.0011		2.14 [1.27, 3.61], 0.0043		2.29 [1.58, 3.34], <0.0001	
OR [95%-CI]; p-value	6.59 [2.56, 17.00], <0.0001		5.36 [2.09, 13.80], 0.0003		5.97 [3.06, 11.64], <0.0001	
RD [95%-CI]; p-value	0.44 [0.25, 0.63], <0.0001		0.39 [0.19, 0.60], 0.0001		0.42 [0.28, 0.56], <0.0001	
Vist 13/ET:n/N1 (%)	39/58 (67.2)	10/33 (30.3)	50/65 (76.9)	10/29 (34.5)	89/123 (72.4)	20/62 (32.3)
RR [95%-CI]; p-value	2.22 [1.28, 3.84], 0.0043		2.23 [1.33, 3.75], 0.0024		2.24 [1.54, 3.27], <0.0001	
OR [95%-CI]; p-value	4.72 [1.88, 11.88], 0.0007		6.33 [2.43, 16.52], <0.0001		5.50 [2.83, 10.67], <0.0001	
RD [95%-CI]; p-value	0.37 [0.17, 0.57], 0.0003		0.42 [0.22, 0.63], <0.0001		0.40 [0.26, 0.54], <0.0001	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
EAP:n/N2 (%)	42/57 (73.7)	6/29 (20.7)	37/54 (68.5)	7/31 (22.6)	79/111 (71.2)	13/60 (21.7)
RR [95%-CI]; p-value	3.56 [1.72, 7.38], 0.0006		3.03 [1.54, 5.97], 0.0013		3.28 [2.00, 5.39], <0.0001	
OR [95%-CI]; p-value	10.73 [3.66, 31.44], <0.0001		7.46 [2.69, 20.68], <0.0001		8.93 [4.26, 18.69], <0.0001	
RD [95%-CI]; p-value	0.53 [0.34, 0.72], <0.0001		0.46 [0.27, 0.65], <0.0001		0.50 [0.36, 0.63], <0.0001	
Vist 13/ET:n/N2 (%)	39/57 (68.4)	5/29 (17.2)	37/54 (68.5)	8/31 (25.8)	76/111 (68.5)	13/60 (21.7)
RR [95%-CI]; p-value	3.97 [1.75, 8.98], 0.0009		2.66 [1.42, 4.95], 0.0021		3.16 [1.92, 5.20], <0.0001	
OR [95%-CI]; p-value	10.40 [3.41, 31.67], <0.0001		6.26 [2.33, 16.81], 0.0001		7.85 [3.77, 16.34], <0.0001	
RD [95%-CI]; p-value	0.51 [0.33, 0.69], <0.0001		0.43 [0.23, 0.62], <0.0001		0.47 [0.33, 0.60], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_2_1_1_2_m_pth10pct_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6108		0.4807		0.8752	
Comparison Baseline vs. EAP	0.5063		0.6511		0.4382	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	20.6 (5.04)	19.4 (5.97)	20.0 (5.76)	19.0 (5.44)	20.3 (5.42)	19.2 (5.69)
Visit 13/ET						
n/N1	58/58	33/33	63/65	27/29	121/123	60/62
Mean (SD)	67.8 (25.15)	18.1 (6.61)	67.2 (19.61)	20.1 (6.61)	67.5 (22.34)	19.0 (6.63)
EAP						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	67.6 (23.96)	18.5 (6.73)	65.5 (20.07)	19.3 (6.11)	66.5 (21.92)	18.9 (6.41)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	47.1 (2.54)	-1.0 (3.37)	47.2 (2.08)	0.4 (3.17)	47.2 (1.64)	-0.4 (2.34)
95% CI	[42.08, 52.18]	[-7.71, 5.70]	[43.12, 51.37]	[-5.89, 6.72]	[44.01, 50.47]	[-4.99, 4.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.13		46.83		47.61	
95% CI	[39.72, 56.54]		[39.30, 54.37]		[41.97, 53.25]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.50		2.81		2.66	
95% CI	[1.94, 3.05]		[2.21, 3.42]		[2.25, 3.08]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (2.46)	-0.7 (3.27)	45.6 (2.06)	0.1 (3.08)	46.3 (1.60)	-0.3 (2.25)
95% CI	[42.07, 51.86]	[-7.22, 5.78]	[41.53, 49.71]	[-6.00, 6.25]	[43.16, 49.46]	[-4.76, 4.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.69		45.50		46.63	
95% CI	[39.53, 55.85]		[38.12, 52.87]		[41.17, 52.08]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.55		2.72		2.65	
95% CI	[1.98, 3.11]		[2.14, 3.30]		[2.24, 3.06]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	19.1 (5.16)	19.1 (5.41)	19.2 (5.31)	19.5 (5.88)	19.2 (5.21)	19.3 (5.62)
Visit 13/ET						
n/N2	57/57	28/29	54/54	30/31	111/111	58/60
Mean (SD)	67.7 (22.69)	16.6 (5.97)	71.6 (25.64)	19.9 (7.31)	69.6 (24.14)	18.3 (6.84)
EAP						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	66.0 (21.06)	16.8 (5.68)	69.4 (21.87)	19.7 (7.02)	67.7 (21.42)	18.3 (6.52)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.2.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.6 (2.48)	-2.6 (3.54)	52.3 (2.82)	0.3 (3.78)	50.5 (1.87)	-1.1 (2.59)
95% CI	[43.64, 53.52]	[-9.65, 4.44]	[46.74, 57.95]	[-7.24, 7.80]	[46.77, 54.15]	[-6.26, 3.96]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.19		52.06		51.61	
95% CI	[42.58, 59.80]		[42.68, 61.45]		[45.31, 57.91]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.71		2.51		2.62	
95% CI	[2.10, 3.32]		[1.93, 3.09]		[2.19, 3.04]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.9 (2.29)	-2.3 (3.21)	50.2 (2.33)	0.2 (3.07)	48.6 (1.63)	-1.1 (2.22)
95% CI	[42.37, 51.47]	[-8.73, 4.03]	[45.58, 54.83]	[-5.91, 6.31]	[45.33, 51.77]	[-5.44, 3.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.27		50.01		49.61	
95% CI	[41.43, 57.10]		[42.34, 57.67]		[44.17, 55.04]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.83		2.91		2.88	
95% CI	[2.22, 3.44]		[2.30, 3.53]		[2.45, 3.32]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_2_1_m_25d_ckd_pp.sas using SAS 9.4

Table 12.3.1.1.s5.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4081		0.2176		0.6624	
Vist 13/ET	0.9360		0.4442		0.4446	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
EAP:n/N1 (%)	55/58 (94.8)	2/33 (6.1)	64/65 (98.5)	1/29 (3.4)	119/123 (96.7)	3/62 (4.8)
RR [95%-CI]; p-value	15.65 [4.08, 60.03], <0.0001		28.55 [4.16, 195.96], 0.0006		19.99 [6.63, 60.33], <0.0001	
OR [95%-CI]; p-value	284.17 [45.02, 1793.83], <0.0001		1792.00 [108.19, 29680.50], <0.0001		585.08 [126.80, 2699.67], <0.0001	
RD [95%-CI]; p-value	0.89 [0.79, 0.99], <0.0001		0.95 [0.88, 1.00], <0.0001		0.92 [0.86, 0.98], <0.0001	
Vist 13/ET:n/N1 (%)	52/58 (89.7)	1/33 (3.0)	63/65 (96.9)	2/29 (6.9)	115/123 (93.5)	3/62 (4.8)
RR [95%-CI]; p-value	29.59 [4.29, 204.25], 0.0006		14.05 [3.69, 53.56], 0.0001		19.32 [6.40, 58.33], <0.0001	
OR [95%-CI]; p-value	277.33 [31.91, 2410.38], <0.0001		425.25 [56.91, 3177.42], <0.0001		282.71 [72.31, 1105.37], <0.0001	
RD [95%-CI]; p-value	0.87 [0.77, 0.96], <0.0001		0.90 [0.80, 1.00], <0.0001		0.89 [0.82, 0.96], <0.0001	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
EAP:n/N2 (%)	55/57 (96.5)	0/29 (0.0)	52/54 (96.3)	4/31 (12.9)	107/111 (96.4)	4/60 (6.7)
RR [95%-CI]; p-value	56.93 [3.64, 889.34], 0.0040		7.46 [2.99, 18.65], <0.0001		14.46 [5.61, 37.29], <0.0001	
OR [95%-CI]; p-value	1595.00 [69.63, 36536.80], <0.0001		175.50 [30.20, 1019.98], <0.0001		374.50 [90.24, 1554.17], <0.0001	
RD [95%-CI]; p-value	0.95 [0.88, 1.00], <0.0001		0.83 [0.71, 0.96], <0.0001		0.90 [0.83, 0.97], <0.0001	
Vist 13/ET:n/N2 (%)	52/57 (91.2)	1/29 (3.4)	52/54 (96.3)	4/31 (12.9)	104/111 (93.7)	5/60 (8.3)
RR [95%-CI]; p-value	26.46 [3.85, 181.83], 0.0009		7.46 [2.99, 18.65], <0.0001		11.24 [4.85, 26.06], <0.0001	
OR [95%-CI]; p-value	291.20 [32.41, 2616.64], <0.0001		175.50 [30.20, 1019.98], <0.0001		163.43 [49.56, 538.95], <0.0001	
RD [95%-CI]; p-value	0.88 [0.78, 0.98], <0.0001		0.83 [0.71, 0.96], <0.0001		0.85 [0.77, 0.94], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_3_1_1_m_25d30_ckd_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3446		0.7001		0.7611	
Comparison Baseline vs. EAP	0.0230		0.6798		0.3301	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	97.9 (9.42)	99.9 (9.86)	100.1 (9.22)	102.7 (7.61)	99.1 (9.31)	101.1 (9.00)
Visit 13/ET						
n/N1	36/36	23/23	47/48	16/16	83/84	39/39
Mean (SD)	85.3 (40.42)	112.6 (43.22)	76.7 (30.29)	113.6 (42.61)	80.5 (35.08)	113.0 (42.41)
EAP						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	84.4 (35.82)	101.8 (34.64)	80.5 (29.62)	110.0 (26.06)	82.1 (32.28)	105.2 (31.29)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-12.6 (6.79)	12.6 (8.50)	-23.2 (4.79)	10.8 (8.25)	-17.9 (4.07)	11.7 (5.99)
95% CI	[-26.16, 1.04]	[-4.43, 29.64]	[-32.80, -13.63]	[-5.70, 27.31]	[-25.94, -9.83]	[-0.17, 23.56]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-25.17		-34.01		-29.58	
95% CI	[-47.02, -3.32]		[-53.17, -14.86]		[-43.97, -15.20]	
p-value	0.0248		0.0007		<0.0001	
Hedges' g	-0.62		-1.03		-0.83	
95% CI	[-1.15, -0.09]		[-1.62, -0.45]		[-1.23, -0.44]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-13.3 (5.60)	1.5 (7.01)	-19.4 (3.84)	6.6 (6.68)	-16.3 (3.31)	4.1 (4.90)
95% CI	[-24.54, -2.10]	[-12.52, 15.58]	[-27.08, -11.71]	[-6.74, 19.99]	[-22.90, -9.78]	[-5.60, 13.81]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-14.85		-26.02		-20.44	
95% CI	[-32.87, 3.18]		[-41.49, -10.55]		[-32.19, -8.69]	
p-value	0.1045		0.0013		0.0008	
Hedges' g	-0.46		-1.00		-0.70	
95% CI	[-0.98, 0.07]		[-1.59, -0.42]		[-1.09, -0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	133.7 (10.99)	133.1 (12.01)	133.0 (12.77)	133.4 (11.95)	133.4 (11.79)	133.3 (11.84)
Visit 13/ET						
n/N2	41/42	22/22	36/37	22/23	77/79	44/45
Mean (SD)	102.1 (33.69)	133.5 (39.56)	113.0 (42.10)	147.1 (59.07)	107.2 (38.00)	140.3 (50.16)
EAP						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	97.4 (27.78)	137.1 (33.13)	111.1 (35.31)	142.5 (39.65)	103.8 (32.06)	139.9 (36.29)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.1 (5.60)	0.3 (7.65)	-19.3 (7.77)	12.9 (9.95)	-25.4 (4.85)	7.0 (6.40)
95% CI	[-42.28, -19.86]	[-15.01, 15.60]	[-34.88, -3.73]	[-7.03, 32.83]	[-35.03, -15.83]	[-5.67, 19.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-31.36		-32.20		-32.43	
95% CI	[-50.33, -12.40]		[-57.52, -6.89]		[-48.32, -16.53]	
p-value	0.0016		0.0136		<0.0001	
Hedges' g	-0.81		-0.70		-0.76	
95% CI	[-1.34, -0.27]		[-1.23, -0.16]		[-1.14, -0.38]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.2 (4.55)	3.8 (6.29)	-21.9 (5.68)	9.0 (7.20)	-29.1 (3.63)	6.5 (4.80)
95% CI	[-45.29, -27.08]	[-8.76, 16.40]	[-33.30, -10.55]	[-5.44, 23.41]	[-36.30, -21.94]	[-2.98, 16.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-40.00		-30.91		-35.63	
95% CI	[-55.53, -24.47]		[-49.28, -12.54]		[-47.54, -23.73]	
p-value	<0.0001		0.0014		<0.0001	
Hedges' g	-1.33		-0.89		-1.11	
95% CI	[-1.89, -0.77]		[-1.43, -0.35]		[-1.50, -0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	201.8 (51.09)	191.8 (31.69)	214.2 (74.73)	215.3 (58.98)	207.7 (63.35)	204.8 (49.55)
Visit 13/ET						
n/N3	37/37	16/17	34/34	20/21	71/71	36/38
Mean (SD)	152.8 (81.15)	221.5 (69.71)	155.8 (143.37)	229.9 (70.46)	154.2 (114.37)	226.1 (69.24)
EAP						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	147.5 (62.88)	219.2 (70.62)	164.5 (121.07)	212.1 (70.37)	155.6 (94.96)	215.3 (69.62)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-48.7 (10.93)	31.7 (16.68)	-58.0 (14.65)	11.6 (19.10)	-53.9 (9.12)	22.9 (12.88)
95% CI	[-70.68, -26.77]		[-87.43, -28.62]		[-71.99, -35.81]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-80.48		-69.66		-76.81	
95% CI	[-120.67, -40.28]		[-117.99, -21.32]		[-108.13, -45.50]	
p-value	0.0002		0.0056		<0.0001	
Hedges' g	-1.22		-0.80		-0.97	
95% CI	[-1.84, -0.60]		[-1.37, -0.24]		[-1.39, -0.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-53.7 (9.03)	25.9 (13.35)	-49.6 (12.05)	-3.3 (15.33)	-52.0 (7.54)	12.2 (10.36)
95% CI	[-71.80, -35.54]		[-73.78, -25.43]		[-66.99, -37.08]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-79.59		-46.33		-64.21	
95% CI	[-112.02, -47.16]		[-85.45, -7.20]		[-89.63, -38.79]	
p-value	<0.0001		0.0212		<0.0001	
Hedges' g	-1.46		-0.65		-0.98	
95% CI	[-2.09, -0.83]		[-1.20, -0.10]		[-1.39, -0.57]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_2_1_m_pth_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.1.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3615		0.8544		0.6823	
Vist 13/ET	0.4599		0.4531		0.2335	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
EAP:n/N1 (%)	11/36 (30.6)	3/23 (13.0)	18/48 (37.5)	1/16 (6.3)	29/84 (34.5)	4/39 (10.3)
RR [95%-CI]; p-value	2.34 [0.73, 7.51], 0.1519		6.00 [0.87, 41.44], 0.0692		3.37 [1.27, 8.91], 0.0146	
OR [95%-CI]; p-value	2.93 [0.72, 11.96], 0.1231		9.00 [1.09, 74.00], 0.0178		4.61 [1.49, 14.25], 0.0047	
RD [95%-CI]; p-value	0.18 [-0.03, 0.38], 0.0924		0.31 [0.13, 0.49], 0.0007		0.24 [0.10, 0.38], 0.0006	
Vist 13/ET:n/N1 (%)	12/36 (33.3)	3/23 (13.0)	24/48 (50.0)	2/16 (12.5)	36/84 (42.9)	5/39 (12.8)
RR [95%-CI]; p-value	2.56 [0.81, 8.09], 0.1104		4.00 [1.06, 15.08], 0.0406		3.34 [1.42, 7.86], 0.0057	
OR [95%-CI]; p-value	3.33 [0.82, 13.48], 0.0809		7.00 [1.43, 34.19], 0.0082		5.10 [1.81, 14.33], 0.0010	
RD [95%-CI]; p-value	0.20 [-0.00, 0.41], 0.0542		0.38 [0.16, 0.59], 0.0006		0.30 [0.15, 0.45], <0.0001	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
EAP:n/N2 (%)	19/42 (45.2)	1/22 (4.5)	11/37 (29.7)	2/23 (8.7)	30/79 (38.0)	3/45 (6.7)
RR [95%-CI]; p-value	9.95 [1.43, 69.51], 0.0205		3.42 [0.83, 14.06], 0.0884		5.70 [1.84, 17.62], 0.0025	
OR [95%-CI]; p-value	17.35 [2.13, 141.11], 0.0009		4.44 [0.89, 22.28], 0.0545		8.57 [2.44, 30.11], 0.0001	
RD [95%-CI]; p-value	0.41 [0.23, 0.58], <0.0001		0.21 [0.02, 0.40], 0.0274		0.31 [0.18, 0.44], <0.0001	
Vist 13/ET:n/N2 (%)	19/42 (45.2)	3/22 (13.6)	11/37 (29.7)	3/23 (13.0)	30/79 (38.0)	6/45 (13.3)
RR [95%-CI]; p-value	3.32 [1.10, 10.00], 0.0331		2.28 [0.71, 7.31], 0.1660		2.85 [1.28, 6.32], 0.0100	
OR [95%-CI]; p-value	5.23 [1.34, 20.40], 0.0115		2.82 [0.69, 11.48], 0.1373		3.98 [1.51, 10.52], 0.0037	
RD [95%-CI]; p-value	0.32 [0.11, 0.52], 0.0029		0.17 [-0.03, 0.37], 0.1047		0.25 [0.10, 0.39], 0.0009	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_1_m_pth30pct_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.1.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
EAP:n/N3 (%)	16/37 (43.2)	1/17 (5.9)	18/34 (52.9)	2/21 (9.5)	34/71 (47.9)	3/38 (7.9)
RR [95%-CI]; p-value	7.35 [1.06, 51.00], 0.0435		5.56 [1.43, 21.57], 0.0131		6.07 [1.99, 18.46], 0.0015	
OR [95%-CI]; p-value	12.19 [1.46, 101.80], 0.0060		10.69 [2.15, 53.21], 0.0011		10.72 [3.02, 38.09], <0.0001	
RD [95%-CI]; p-value	0.37 [0.18, 0.57], 0.0002		0.43 [0.22, 0.64], <0.0001		0.40 [0.26, 0.54], <0.0001	
Vist 13/ET:n/N3 (%)	18/37 (48.6)	0/17 (0.0)	23/34 (67.6)	2/21 (9.5)	41/71 (57.7)	2/38 (5.3)
RR [95%-CI]; p-value	17.03 [1.09, 266.86], 0.0435		7.10 [1.86, 27.09], 0.0041		10.97 [2.81, 42.90], 0.0006	
OR [95%-CI]; p-value	32.21 [1.80, 576.81], 0.0009		19.86 [3.91, 100.83], <0.0001		24.60 [5.49, 110.22], <0.0001	
RD [95%-CI]; p-value	0.46 [0.28, 0.64], <0.0001		0.58 [0.38, 0.78], <0.0001		0.52 [0.39, 0.66], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_1_m_pth30pct_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.2.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3116		0.9619		0.5745	
Vist 13/ET	0.2436		0.3832		0.1485	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
EAP:n/N1 (%)	25/36 (69.4)	8/23 (34.8)	36/48 (75.0)	5/16 (31.3)	61/84 (72.6)	13/39 (33.3)
RR [95%-CI]; p-value	2.00 [1.10, 3.64], 0.0239		2.40 [1.14, 5.05], 0.0213		2.18 [1.37, 3.46], 0.0010	
OR [95%-CI]; p-value	4.26 [1.40, 12.97], 0.0089		6.60 [1.90, 22.87], 0.0016		5.30 [2.34, 12.05], <0.0001	
RD [95%-CI]; p-value	0.35 [0.10, 0.59], 0.0058		0.44 [0.18, 0.70], 0.0009		0.39 [0.22, 0.57], <0.0001	
Vist 13/ET:n/N1 (%)	25/36 (69.4)	6/23 (26.1)	34/48 (70.8)	6/16 (37.5)	59/84 (70.2)	12/39 (30.8)
RR [95%-CI]; p-value	2.66 [1.29, 5.48], 0.0078		1.89 [0.98, 3.65], 0.0582		2.28 [1.40, 3.73], 0.0010	
OR [95%-CI]; p-value	6.44 [2.00, 20.75], 0.0011		4.05 [1.23, 13.28], 0.0171		5.31 [2.33, 12.12], <0.0001	
RD [95%-CI]; p-value	0.43 [0.20, 0.67], 0.0003		0.33 [0.06, 0.60], 0.0155		0.39 [0.22, 0.57], <0.0001	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
EAP:n/N2 (%)	35/42 (83.3)	6/22 (27.3)	22/37 (59.5)	5/23 (21.7)	57/79 (72.2)	11/45 (24.4)
RR [95%-CI]; p-value	3.06 [1.52, 6.13], 0.0016		2.74 [1.20, 6.21], 0.0161		2.95 [1.73, 5.02], <0.0001	
OR [95%-CI]; p-value	13.33 [3.86, 46.10], <0.0001		5.28 [1.61, 17.33], 0.0043		8.01 [3.46, 18.53], <0.0001	
RD [95%-CI]; p-value	0.56 [0.34, 0.78], <0.0001		0.38 [0.15, 0.61], 0.0014		0.48 [0.32, 0.64], <0.0001	
Vist 13/ET:n/N2 (%)	30/42 (71.4)	8/22 (36.4)	23/37 (62.2)	7/23 (30.4)	53/79 (67.1)	15/45 (33.3)
RR [95%-CI]; p-value	1.96 [1.09, 3.53], 0.0237		2.04 [1.05, 3.98], 0.0359		2.01 [1.29, 3.13], 0.0019	
OR [95%-CI]; p-value	4.38 [1.46, 13.10], 0.0067		3.76 [1.24, 11.38], 0.0169		4.08 [1.87, 8.87], 0.0003	
RD [95%-CI]; p-value	0.35 [0.11, 0.59], 0.0047		0.32 [0.07, 0.56], 0.0110		0.34 [0.17, 0.51], 0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_2_m_pth10pct_ttlpth_pp.sas using SAS 9.4

Table 12.2.1.1.2.s6.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
EAP:n/N3 (%)	25/37 (67.6)	2/17 (11.8)	27/34 (79.4)	7/21 (33.3)	52/71 (73.2)	9/38 (23.7)
RR [95%-CI]; p-value	5.74 [1.53, 21.52], 0.0095		2.38 [1.27, 4.47], 0.0068		3.09 [1.72, 5.57], 0.0002	
OR [95%-CI]; p-value	15.63 [3.07, 79.59], 0.0001		7.71 [2.25, 26.41], 0.0006		8.82 [3.54, 22.00], <0.0001	
RD [95%-CI]; p-value	0.56 [0.34, 0.77], <0.0001		0.46 [0.22, 0.70], 0.0002		0.50 [0.33, 0.67], <0.0001	
Vist 13/ET:n/N3 (%)	23/37 (62.2)	1/17 (5.9)	30/34 (88.2)	5/21 (23.8)	53/71 (74.6)	6/38 (15.8)
RR [95%-CI]; p-value	10.57 [1.55, 71.94], 0.0160		3.71 [1.71, 8.04], 0.0009		4.73 [2.24, 9.98], <0.0001	
OR [95%-CI]; p-value	26.29 [3.13, 220.47], 0.0001		24.00 [5.64, 102.11], <0.0001		15.70 [5.65, 43.67], <0.0001	
RD [95%-CI]; p-value	0.56 [0.37, 0.75], <0.0001		0.64 [0.43, 0.86], <0.0001		0.59 [0.43, 0.74], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_2_1_1_2_m_pth10pct_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3632		0.6757		0.2671	
Comparison Baseline vs. EAP	0.9311		0.7857		0.8568	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	20.3 (5.20)	20.8 (6.16)	20.7 (5.37)	21.6 (5.44)	20.5 (5.27)	21.1 (5.82)
Visit 13/ET						
n/N1	36/36	23/23	47/48	16/16	83/84	39/39
Mean (SD)	68.8 (26.04)	18.0 (6.68)	71.2 (21.45)	20.8 (5.53)	70.1 (23.43)	19.2 (6.30)
EAP						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	66.7 (23.64)	18.7 (6.52)	70.5 (20.27)	21.1 (6.37)	68.9 (21.72)	19.7 (6.49)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.5 (3.30)	-2.8 (4.13)	50.3 (2.75)	-0.5 (4.71)	49.4 (2.14)	-1.7 (3.15)
95% CI	[41.90, 55.14]	[-11.08, 5.49]	[44.76, 55.76]	[-9.93, 8.93]	[45.14, 53.63]	[-7.94, 4.54]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.31		50.76		51.09	
95% CI	[40.71, 61.92]		[39.84, 61.68]		[43.53, 58.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.57		2.67		2.67	
95% CI	[1.87, 3.26]		[1.94, 3.40]		[2.17, 3.18]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.4 (3.03)	-2.1 (3.79)	49.8 (2.54)	-0.3 (4.40)	48.1 (1.96)	-1.2 (2.90)
95% CI	[40.37, 52.50]	[-9.69, 5.49]	[44.73, 54.89]	[-9.11, 8.50]	[44.24, 52.01]	[-6.98, 4.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	48.54		50.12		49.36	
95% CI	[38.82, 58.25]		[39.94, 60.30]		[42.41, 56.30]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.66		2.84		2.80	
95% CI	[1.95, 3.36]		[2.10, 3.59]		[2.29, 3.32]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	19.8 (4.72)	17.7 (5.49)	20.0 (5.87)	19.3 (5.22)	19.9 (5.26)	18.5 (5.35)
Visit 13/ET						
n/N2	42/42	22/22	36/37	22/23	78/79	44/45
Mean (SD)	69.5 (20.30)	16.2 (5.76)	62.8 (17.17)	20.5 (6.96)	66.4 (19.10)	18.3 (6.67)
EAP						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	68.8 (21.27)	16.6 (6.28)	60.5 (16.52)	19.4 (5.77)	64.9 (19.53)	18.1 (6.12)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	50.2 (2.62)	-2.3 (3.65)	43.0 (2.32)	0.9 (2.96)	46.5 (1.76)	-0.6 (2.34)
95% CI	[44.91, 55.40]	[-9.61, 4.98]	[38.34, 47.63]	[-5.08, 6.80]	[43.04, 50.03]	[-5.28, 4.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	52.47		42.12		47.17	
95% CI	[43.40, 61.54]		[34.58, 49.66]		[41.34, 53.00]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.96		2.97		2.95	
95% CI	[2.24, 3.69]		[2.22, 3.73]		[2.43, 3.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	49.6 (2.76)	-2.1 (3.84)	40.5 (2.12)	0.1 (2.69)	45.0 (1.76)	-0.8 (2.34)
95% CI	[44.07, 55.13]	[-9.78, 5.60]	[36.27, 44.75]	[-5.29, 5.47]	[41.49, 48.48]	[-5.48, 3.79]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.69		40.42		45.83	
95% CI	[42.13, 61.25]		[33.57, 47.28]		[40.00, 51.66]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.74		3.10		2.82	
95% CI	[2.04, 3.44]		[2.35, 3.86]		[2.32, 3.33]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	19.5 (5.59)	19.3 (4.90)	17.7 (5.09)	17.5 (5.84)	18.6 (5.39)	18.3 (5.44)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	64.9 (25.71)	18.1 (6.68)	73.3 (27.81)	18.8 (8.05)	68.9 (26.88)	18.5 (7.36)
EAP						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	64.6 (23.08)	17.8 (6.06)	70.1 (24.56)	18.4 (7.48)	67.3 (23.79)	18.1 (6.80)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.2.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	45.4 (3.42)	-1.3 (5.19)	55.7 (3.72)	0.5 (4.97)	50.5 (2.51)	-0.4 (3.58)
95% CI	[38.52, 52.25]		[48.19, 63.11]		[45.54, 55.49]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.67		55.12		50.88	
95% CI	[34.19, 59.16]		[42.65, 67.59]		[42.21, 59.56]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.23		2.50		2.35	
95% CI	[1.51, 2.94]		[1.77, 3.23]		[1.84, 2.86]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	45.1 (2.98)	-1.4 (4.39)	52.4 (3.20)	0.9 (4.07)	48.8 (2.17)	-0.3 (2.98)
95% CI	[39.17, 51.12]		[45.97, 58.80]		[44.45, 53.07]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	46.58		51.52		49.05	
95% CI	[35.92, 57.23]		[41.13, 61.91]		[41.73, 56.37]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.54		2.74		2.63	
95% CI	[1.80, 3.29]		[1.99, 3.48]		[2.11, 3.16]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_2_1_m_25d_ttlpth_pp.sas using SAS 9.4

Table 12.3.1.1.s6.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.9697		0.4323		0.4866	
Vist 13/ET	0.8289		0.6806		0.3890	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
EAP:n/N1 (%)	35/36 (97.2)	1/23 (4.3)	48/48 (100.0)	2/16 (12.5)	83/84 (98.8)	3/39 (7.7)
RR [95%-CI]; p-value	22.36 [3.29, 152.17], 0.0015		7.92 [2.16, 28.96], 0.0018		12.85 [4.33, 38.11], <0.0001	
OR [95%-CI]; p-value	770.00 [45.78, 12952.30], <0.0001		672.00 [28.63, 15770.54], <0.0001		996.00 [100.19, 9901.78], <0.0001	
RD [95%-CI]; p-value	0.93 [0.83, 1.00], <0.0001		0.86 [0.70, 1.00], <0.0001		0.91 [0.82, 1.00], <0.0001	
Vist 13/ET:n/N1 (%)	32/36 (88.9)	0/23 (0.0)	47/48 (97.9)	1/16 (6.3)	79/84 (94.0)	1/39 (2.6)
RR [95%-CI]; p-value	41.78 [2.69, 649.99], 0.0077		15.67 [2.35, 104.55], 0.0045		36.68 [5.30, 254.07], 0.0003	
OR [95%-CI]; p-value	368.00 [18.54, 7306.00], <0.0001		705.00 [41.52, 11971.57], <0.0001		600.40 [67.76, 5319.94], <0.0001	
RD [95%-CI]; p-value	0.87 [0.75, 0.99], <0.0001		0.92 [0.79, 1.00], <0.0001		0.91 [0.84, 0.99], <0.0001	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
EAP:n/N2 (%)	41/42 (97.6)	1/22 (4.5)	36/37 (97.3)	0/23 (0.0)	77/79 (97.5)	1/45 (2.2)
RR [95%-CI]; p-value	21.48 [3.16, 145.83], 0.0017		45.73 [2.94, 710.12], 0.0063		43.86 [6.31, 304.73], 0.0001	
OR [95%-CI]; p-value	861.00 [51.26, 14463.16], <0.0001		1656.00 [53.37, 51379.63], <0.0001		1694.00 [149.30, 19220.11], <0.0001	
RD [95%-CI]; p-value	0.93 [0.83, 1.00], <0.0001		0.95 [0.87, 1.00], <0.0001		0.95 [0.90, 1.00], <0.0001	
Vist 13/ET:n/N2 (%)	40/42 (95.2)	1/22 (4.5)	36/37 (97.3)	2/23 (8.7)	76/79 (96.2)	3/45 (6.7)
RR [95%-CI]; p-value	20.95 [3.08, 142.36], 0.0019		11.19 [2.97, 42.11], 0.0004		14.43 [4.83, 43.10], <0.0001	
OR [95%-CI]; p-value	420.00 [35.96, 4905.59], <0.0001		378.00 [32.29, 4424.62], <0.0001		354.67 [68.52, 1835.83], <0.0001	
RD [95%-CI]; p-value	0.91 [0.80, 1.00], <0.0001		0.89 [0.76, 1.00], <0.0001		0.90 [0.81, 0.98], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_1_1_m_25d30_ttlpth_pp.sas using SAS 9.4

Table 12.3.1.1.s6.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
EAP:n/N3 (%)	34/37 (91.9)	0/17 (0.0)	32/34 (94.1)	3/21 (14.3)	66/71 (93.0)	3/38 (7.9)
RR [95%-CI]; p-value	32.16 [2.09, 494.92], 0.0128		6.59 [2.30, 18.85], 0.0004		11.77 [3.97, 34.95], <0.0001	
OR [95%-CI]; p-value	385.33 [18.25, 8136.25], <0.0001		96.00 [14.65, 629.18], <0.0001		154.00 [34.75, 682.54], <0.0001	
RD [95%-CI]; p-value	0.89 [0.77, 1.00], <0.0001		0.80 [0.63, 0.97], <0.0001		0.85 [0.75, 0.95], <0.0001	
Vist 13/ET:n/N3 (%)	32/37 (86.5)	1/17 (5.9)	32/34 (94.1)	3/21 (14.3)	64/71 (90.1)	4/38 (10.5)
RR [95%-CI]; p-value	14.70 [2.19, 98.86], 0.0057		6.59 [2.30, 18.85], 0.0004		8.56 [3.38, 21.71], <0.0001	
OR [95%-CI]; p-value	102.40 [11.02, 951.66], <0.0001		96.00 [14.65, 629.18], <0.0001		77.71 [21.24, 284.30], <0.0001	
RD [95%-CI]; p-value	0.81 [0.65, 0.96], <0.0001		0.80 [0.63, 0.97], <0.0001		0.80 [0.68, 0.92], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_3_1_1_m_25d30_ttlpth_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3935		0.4470		0.8993	
Comparison Baseline vs. EAP	0.2151		0.3589		0.1764	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	156.5 (78.86)	99.7 (11.50)	114.2 (24.99)	120.9 (32.62)	127.9 (52.27)	109.1 (24.29)
Visit 13/ET						
n/N1	13/13	5/5	27/27	3/4	40/40	8/9
Mean (SD)	129.3 (80.40)	106.4 (45.36)	86.6 (39.97)	119.3 (27.57)	100.5 (58.86)	111.3 (37.92)
EAP						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	129.1 (67.71)	96.5 (41.58)	90.1 (39.15)	104.9 (20.58)	102.8 (52.68)	100.2 (32.30)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-20.7 (17.88)	-10.2 (29.77)	-27.4 (6.62)	13.0 (19.97)	-23.0 (8.03)	2.7 (17.24)
95% CI	[-58.78, 17.45]	[-73.65, 53.25]	[-41.02, -13.86]	[-27.97, 53.97]	[-39.23, -6.84]	[-32.05, 37.49]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-10.47		-40.44		-25.75	
95% CI	[-86.56, 65.62]		[-83.65, 2.78]		[-64.72, 13.22]	
p-value	0.7733		0.0655		0.1897	
Hedges' g	-0.48		-1.20		-0.76	
95% CI	[-1.47, 0.52]		[-2.40, -0.00]		[-1.52, -0.00]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-21.6 (12.97)	-18.1 (21.60)	-24.5 (6.70)	-13.7 (17.47)	-21.7 (6.65)	-14.8 (13.06)
95% CI	[-49.27, 6.03]	[-64.16, 27.91]	[-38.19, -10.72]	[-49.49, 22.09]	[-35.12, -8.32]	[-41.16, 11.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-3.50		-10.76		-6.88	
95% CI	[-58.70, 51.71]		[-49.12, 27.61]		[-36.74, 22.98]	
p-value	0.8944		0.5704		0.6448	
Hedges' g	-0.45		-0.22		-0.39	
95% CI	[-1.44, 0.54]		[-1.25, 0.80]		[-1.11, 0.33]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	142.9 (47.70)	140.2 (41.45)	151.3 (67.41)	156.3 (59.77)	146.9 (57.89)	148.1 (51.76)
Visit 13/ET						
n/N2	101/102	56/57	90/92	55/56	191/194	111/113
Mean (SD)	111.2 (59.09)	152.5 (67.24)	118.2 (97.37)	169.0 (76.94)	114.5 (79.32)	160.7 (72.35)
EAP						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	107.0 (48.79)	150.9 (66.34)	121.0 (84.58)	162.0 (65.28)	113.6 (68.33)	156.4 (65.76)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.4 (4.81)	13.7 (6.47)	-33.7 (6.70)	12.1 (8.58)	-32.6 (4.07)	13.1 (5.33)
95% CI	[-40.91, -21.90]	[0.93, 26.47]	[-46.97, -20.47]	[-4.82, 29.09]	[-40.66, -24.64]	[2.61, 23.59]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.10		-45.85		-45.75	
95% CI	[-61.03, -29.18]		[-67.38, -24.33]		[-58.95, -32.55]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.94		-0.72		-0.81	
95% CI	[-1.28, -0.60]		[-1.06, -0.37]		[-1.06, -0.57]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-35.8 (4.06)	10.5 (5.43)	-30.5 (5.15)	5.9 (6.60)	-33.2 (3.25)	8.3 (4.26)
95% CI	[-43.80, -27.75]	[-0.28, 21.18]	[-40.62, -20.28]	[-7.11, 18.97]	[-39.56, -26.76]	[-0.05, 16.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-46.23		-36.38		-41.49	
95% CI	[-59.63, -32.82]		[-52.92, -19.84]		[-52.02, -30.95]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.12		-0.73		-0.91	
95% CI	[-1.46, -0.77]		[-1.07, -0.39]		[-1.15, -0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_2_1_m_pth_dose_pp.sas using SAS 9.4

Table 12.2.1.1.1.s7.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.0863		0.1950		0.0509	
Vist 13/ET	0.3747		0.8869		0.9993	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
EAP:n/N1 (%)	2/13 (15.4)	1/5 (20.0)	10/27 (37.0)	1/4 (25.0)	12/40 (30.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.77 [0.09, 6.72], 0.8125		1.48 [0.25, 8.67], 0.6629		1.35 [0.36, 5.01], 0.6536	
OR [95%-CI]; p-value	0.73 [0.05, 10.39], 0.8139		1.76 [0.16, 19.34], 0.6387		1.50 [0.27, 8.30], 0.6407	
RD [95%-CI]; p-value	-0.05 [-0.45, 0.36], 0.8218		0.12 [-0.34, 0.58], 0.6094		0.08 [-0.23, 0.38], 0.6189	
Vist 13/ET:n/N1 (%)	5/13 (38.5)	1/5 (20.0)	14/27 (51.9)	0/4 (0.0)	19/40 (47.5)	1/9 (11.1)
RR [95%-CI]; p-value	1.92 [0.29, 12.64], 0.4961		4.67 [0.33, 65.29], 0.2525		4.28 [0.65, 27.91], 0.1291	
OR [95%-CI]; p-value	2.50 [0.21, 29.25], 0.4568		8.62 [0.41, 179.27], 0.1084		7.24 [0.83, 63.36], 0.0448	
RD [95%-CI]; p-value	0.18 [-0.25, 0.62], 0.4100		0.41 [0.06, 0.75], 0.0211		0.36 [0.11, 0.62], 0.0055	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
EAP:n/N2 (%)	44/102 (43.1)	4/57 (7.0)	37/92 (40.2)	4/56 (7.1)	81/194 (41.8)	8/113 (7.1)
RR [95%-CI]; p-value	6.15 [2.33, 16.23], 0.0002		5.63 [2.12, 14.95], 0.0005		5.90 [2.96, 11.74], <0.0001	
OR [95%-CI]; p-value	10.05 [3.38, 29.87], <0.0001		8.75 [2.91, 26.25], <0.0001		9.41 [4.34, 20.39], <0.0001	
RD [95%-CI]; p-value	0.36 [0.24, 0.48], <0.0001		0.33 [0.21, 0.45], <0.0001		0.35 [0.26, 0.43], <0.0001	
Vist 13/ET:n/N2 (%)	44/102 (43.1)	5/57 (8.8)	44/92 (47.8)	7/56 (12.5)	88/194 (45.4)	12/113 (10.6)
RR [95%-CI]; p-value	4.92 [2.07, 11.70], 0.0003		3.83 [1.85, 7.90], 0.0003		4.27 [2.45, 7.45], <0.0001	
OR [95%-CI]; p-value	7.89 [2.91, 21.40], <0.0001		6.42 [2.63, 15.65], <0.0001		6.99 [3.60, 13.54], <0.0001	
RD [95%-CI]; p-value	0.34 [0.22, 0.46], <0.0001		0.35 [0.22, 0.49], <0.0001		0.35 [0.26, 0.44], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_1_1_1_m_pth30pct_dose_pp.sas using SAS 9.4

Table 12.2.1.1.2.s7.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.3697		0.3050		0.1885	
Vist 13/ET	0.8217		0.8143		0.8625	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
EAP:n/N1 (%)	9/13 (69.2)	2/5 (40.0)	20/27 (74.1)	2/4 (50.0)	29/40 (72.5)	4/9 (44.4)
RR [95%-CI]; p-value	1.73 [0.56, 5.37], 0.3427		1.48 [0.54, 4.05], 0.4434		1.63 [0.77, 3.47], 0.2039	
OR [95%-CI]; p-value	3.38 [0.40, 28.74], 0.2545		2.86 [0.34, 24.30], 0.3222		3.30 [0.75, 14.57], 0.1049	
RD [95%-CI]; p-value	0.29 [-0.21, 0.79], 0.2493		0.24 [-0.28, 0.76], 0.3615		0.28 [-0.07, 0.63], 0.1192	
Vist 13/ET:n/N1 (%)	6/13 (46.2)	1/5 (20.0)	20/27 (74.1)	1/4 (25.0)	26/40 (65.0)	2/9 (22.2)
RR [95%-CI]; p-value	2.31 [0.36, 14.66], 0.3753		2.96 [0.53, 16.41], 0.2137		2.93 [0.84, 10.14], 0.0906	
OR [95%-CI]; p-value	3.43 [0.30, 39.64], 0.3080		8.57 [0.76, 96.52], 0.0501		6.50 [1.19, 35.60], 0.0191	
RD [95%-CI]; p-value	0.26 [-0.18, 0.70], 0.2474		0.49 [0.04, 0.95], 0.0347		0.43 [0.12, 0.74], 0.0067	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
EAP:n/N2 (%)	76/102 (74.5)	14/57 (24.6)	65/92 (70.7)	15/56 (26.8)	141/194 (72.7)	29/113 (25.7)
RR [95%-CI]; p-value	3.03 [1.90, 4.85], <0.0001		2.64 [1.68, 4.15], <0.0001		2.83 [2.05, 3.92], <0.0001	
OR [95%-CI]; p-value	8.98 [4.24, 19.00], <0.0001		6.58 [3.13, 13.82], <0.0001		7.71 [4.55, 13.05], <0.0001	
RD [95%-CI]; p-value	0.50 [0.36, 0.64], <0.0001		0.44 [0.29, 0.59], <0.0001		0.47 [0.37, 0.57], <0.0001	
Vist 13/ET:n/N2 (%)	72/102 (70.6)	14/57 (24.6)	67/92 (72.8)	17/56 (30.4)	139/194 (71.6)	31/113 (27.4)
RR [95%-CI]; p-value	2.87 [1.79, 4.61], <0.0001		2.40 [1.58, 3.64], <0.0001		2.61 [1.91, 3.57], <0.0001	
OR [95%-CI]; p-value	7.37 [3.52, 15.42], <0.0001		6.15 [2.96, 12.78], <0.0001		6.69 [3.98, 11.22], <0.0001	
RD [95%-CI]; p-value	0.46 [0.32, 0.60], <0.0001		0.42 [0.27, 0.58], <0.0001		0.44 [0.34, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_2_1_1_2_m_pth10pct_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3195		0.6183		0.8555	
Comparison Baseline vs. EAP	0.2169		0.8128		0.3754	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	19.3 (5.12)	17.5 (6.97)	22.0 (5.80)	19.2 (6.21)	21.1 (5.66)	18.2 (6.29)
Visit 13/ET						
n/N1	13/13	5/5	27/27	3/4	40/40	8/9
Mean (SD)	52.7 (19.53)	18.8 (7.98)	65.0 (16.48)	18.0 (5.29)	61.0 (18.23)	18.5 (6.68)
EAP						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	52.4 (19.21)	20.0 (8.03)	64.6 (17.97)	16.9 (5.33)	60.6 (19.05)	18.6 (6.74)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	32.9 (3.95)	2.5 (6.40)	43.0 (2.96)	-4.2 (8.89)	38.2 (2.54)	-1.2 (5.50)
95% CI	[24.52, 41.34]	[-11.11, 16.15]	[36.91, 49.06]	[-22.43, 14.03]	[33.11, 43.35]	[-12.29, 9.91]
Diff in LS-Mean [ER-Calcifediol - Placebo]	30.41		47.19		39.42	
95% CI	[14.32, 46.50]		[27.97, 66.41]		[27.20, 51.63]	
p-value	0.0011		<0.0001		<0.0001	
Hedges' g	2.09		3.04		2.62	
95% CI	[0.89, 3.28]		[1.65, 4.43]		[1.71, 3.53]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	32.6 (3.86)	3.7 (6.25)	42.7 (3.15)	-2.2 (8.27)	37.8 (2.62)	0.8 (5.29)
95% CI	[24.37, 40.82]	[-9.67, 16.99]	[36.21, 49.12]	[-19.17, 14.73]	[32.55, 43.12]	[-9.85, 11.48]
Diff in LS-Mean [ER-Calcifediol - Placebo]	28.94		44.88		37.02	
95% CI	[13.20, 44.67]		[26.69, 63.08]		[25.11, 48.94]	
p-value	0.0014		<0.0001		<0.0001	
Hedges' g	2.03		2.72		2.45	
95% CI	[0.85, 3.22]		[1.49, 3.95]		[1.59, 3.31]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	19.9 (5.15)	19.4 (5.59)	18.9 (5.31)	19.3 (5.65)	19.4 (5.24)	19.3 (5.60)
Visit 13/ET						
n/N2	102/102	56/57	90/92	54/56	192/194	110/113
Mean (SD)	69.7 (23.75)	17.3 (6.22)	70.5 (24.06)	20.1 (7.03)	70.1 (23.84)	18.7 (6.75)
EAP						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	68.7 (22.28)	17.5 (6.14)	68.1 (21.71)	19.7 (6.62)	68.4 (21.96)	18.6 (6.45)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.2.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.8 (1.88)	-2.2 (2.53)	51.5 (2.01)	0.7 (2.60)	50.7 (1.37)	-0.8 (1.81)
95% CI	[46.09, 53.51]	[-7.21, 2.80]	[47.56, 55.51]	[-4.46, 5.81]	[47.97, 53.37]	[-4.34, 2.78]
Diff in LS-Mean [ER-Calcifediol - Placebo]	52.01		50.87		51.45	
95% CI	[45.78, 58.24]		[44.37, 57.36]		[46.98, 55.92]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.74		2.67		2.71	
95% CI	[2.29, 3.18]		[2.21, 3.12]		[2.39, 3.03]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	48.8 (1.77)	-2.0 (2.36)	49.1 (1.76)	0.4 (2.26)	48.9 (1.25)	-0.7 (1.63)
95% CI	[45.30, 52.27]	[-6.63, 2.70]	[45.64, 52.61]	[-4.04, 4.88]	[46.49, 51.40]	[-3.96, 2.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.75		48.70		49.69	
95% CI	[44.92, 56.58]		[43.04, 54.36]		[45.65, 53.73]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.83		2.88		2.86	
95% CI	[2.38, 3.28]		[2.41, 3.35]		[2.54, 3.19]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_2_1_m_25d_dose_pp.sas using SAS 9.4

Table 12.3.1.1.s7.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.0644		0.8842		0.4775	
Vist 13/ET	0.4999		0.9941		0.8245	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
EAP:n/N1 (%)	12/13 (92.3)	1/5 (20.0)	27/27 (100.0)	0/4 (0.0)	39/40 (97.5)	1/9 (11.1)
RR [95%-CI]; p-value	4.62 [0.79, 26.83], 0.0885		8.84 [0.65, 120.62], 0.1023		8.78 [1.38, 55.73], 0.0213	
OR [95%-CI]; p-value	48.00 [2.40, 958.24], 0.0022		432.00 [7.47, 24998.29], <0.0001		312.00 [17.61, 5526.46], <0.0001	
RD [95%-CI]; p-value	0.72 [0.34, 1.00], 0.0002		0.87 [0.58, 1.00], <0.0001		0.86 [0.65, 1.00], <0.0001	
Vist 13/ET:n/N1 (%)	11/13 (84.6)	0/5 (0.0)	27/27 (100.0)	0/4 (0.0)	38/40 (95.0)	0/9 (0.0)
RR [95%-CI]; p-value	9.31 [0.66, 132.13], 0.0993		8.84 [0.65, 120.62], 0.1023		18.05 [1.21, 268.26], 0.0356	
OR [95%-CI]; p-value	55.00 [2.08, 1453.39], 0.0022		432.00 [7.47, 24998.29], <0.0001		342.00 [14.18, 8248.80], <0.0001	
RD [95%-CI]; p-value	0.76 [0.45, 1.00], <0.0001		0.87 [0.58, 1.00], <0.0001		0.90 [0.74, 1.00], <0.0001	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
EAP:n/N2 (%)	98/102 (96.1)	1/57 (1.8)	89/92 (96.7)	5/56 (8.9)	187/194 (96.4)	6/113 (5.3)
RR [95%-CI]; p-value	54.76 [7.85, 382.27], <0.0001		10.83 [4.69, 25.03], <0.0001		18.15 [8.33, 39.57], <0.0001	
OR [95%-CI]; p-value	1372.00 [149.64, 12579.09], <0.0001		302.60 [69.43, 1318.93], <0.0001		476.40 [156.06, 1454.29], <0.0001	
RD [95%-CI]; p-value	0.94 [0.89, 0.99], <0.0001		0.88 [0.80, 0.96], <0.0001		0.91 [0.86, 0.96], <0.0001	
Vist 13/ET:n/N2 (%)	93/102 (91.2)	2/57 (3.5)	88/92 (95.7)	6/56 (10.7)	181/194 (93.3)	8/113 (7.1)
RR [95%-CI]; p-value	25.99 [6.65, 101.52], <0.0001		8.93 [4.19, 19.04], <0.0001		13.18 [6.75, 25.73], <0.0001	
OR [95%-CI]; p-value	284.17 [59.24, 1363.20], <0.0001		183.33 [49.37, 680.76], <0.0001		182.74 [73.34, 455.33], <0.0001	
RD [95%-CI]; p-value	0.88 [0.80, 0.95], <0.0001		0.85 [0.76, 0.94], <0.0001		0.86 [0.80, 0.92], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_3_1_1_m_25d30_dose_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6567		0.5498		0.3113	
Comparison Baseline vs. EAP	0.4305		0.3930		0.1301	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	164.9 (57.31)	123.8 (31.83)	147.6 (64.09)	145.2 (30.11)	155.2 (60.91)	133.3 (32.08)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	116.7 (48.97)	117.6 (40.67)	128.0 (141.99)	179.1 (81.88)	123.0 (109.76)	144.9 (68.01)
EAP						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	114.3 (53.87)	115.5 (43.58)	134.9 (131.63)	171.3 (59.47)	125.8 (103.87)	140.3 (57.24)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-36.6 (11.92)	-23.6 (14.85)	-20.1 (19.00)	35.1 (29.28)	-35.2 (13.39)	15.9 (18.42)
95% CI	[-61.32, -11.87]	[-54.44, 7.16]	[-59.31, 19.11]	[-25.30, 95.57]	[-62.16, -8.30]	[-21.18, 52.94]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-12.95		-55.23		-51.11	
95% CI	[-54.01, 28.11]		[-127.28, 16.81]		[-97.36, -4.87]	
p-value	0.5198		0.1267		0.0310	
Hedges' g	-0.73		-0.57		-0.56	
95% CI	[-1.53, 0.07]		[-1.38, 0.25]		[-1.14, 0.01]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-41.5 (12.34)	-22.1 (15.37)	-13.1 (17.20)	27.0 (26.51)	-32.7 (12.04)	10.4 (16.57)
95% CI	[-67.12, -15.92]	[-53.96, 9.81]	[-48.61, 22.39]	[-27.69, 81.73]	[-56.93, -8.50]	[-22.90, 43.75]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-19.45		-40.13		-43.15	
95% CI	[-61.95, 23.06]		[-105.36, 25.09]		[-84.73, -1.56]	
p-value	0.3530		0.2163		0.0423	
Hedges' g	-0.78		-0.47		-0.51	
95% CI	[-1.58, 0.03]		[-1.28, 0.34]		[-1.08, 0.06]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	141.4 (50.58)	139.4 (42.73)	142.0 (62.29)	155.2 (62.20)	141.7 (56.60)	147.3 (53.69)
Visit 13/ET						
n/N2	99/100	51/52	98/100	50/52	197/200	101/104
Mean (SD)	112.7 (63.63)	154.8 (69.31)	107.6 (74.38)	164.4 (75.56)	110.2 (69.05)	159.5 (72.27)
EAP						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	108.7 (51.25)	152.5 (68.37)	110.0 (62.69)	156.2 (65.90)	109.4 (57.12)	154.3 (66.84)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-28.4 (4.94)	17.1 (6.89)	-35.3 (5.18)	9.9 (7.26)	-31.8 (3.57)	13.4 (4.99)
95% CI	[-38.17, -18.64]	[3.51, 30.73]	[-45.58, -25.11]	[-4.45, 24.25]	[-38.84, -24.79]	[3.58, 23.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.52		-45.24		-45.21	
95% CI	[-62.28, -28.77]		[-62.91, -27.57]		[-57.29, -33.14]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-0.93		-0.84		-0.88	
95% CI	[-1.28, -0.58]		[-1.19, -0.49]		[-1.13, -0.64]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.5 (3.99)	12.9 (5.53)	-32.8 (3.73)	2.4 (5.18)	-32.6 (2.73)	7.6 (3.78)
95% CI	[-40.41, -24.65]	[1.98, 23.85]	[-40.12, -25.39]	[-7.86, 12.61]	[-37.97, -27.24]	[0.13, 15.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-45.45		-35.13		-40.18	
95% CI	[-58.92, -31.97]		[-47.77, -22.49]		[-49.36, -31.00]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	-1.13		-0.85		-0.99	
95% CI	[-1.49, -0.77]		[-1.20, -0.50]		[-1.24, -0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_2_1_m_pth_vitd_pp.sas using SAS 9.4

Table 12.2.1.1.1.s8.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.1722		0.6985		0.6761	
Vist 13/ET	0.9513		0.5815		0.4571	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
EAP:n/N1 (%)	6/15 (40.0)	2/10 (20.0)	8/19 (42.1)	0/8 (0.0)	14/34 (41.2)	2/18 (11.1)
RR [95%-CI]; p-value	2.00 [0.50, 8.00], 0.3270		7.16 [0.46, 110.88], 0.1592		3.71 [0.94, 14.54], 0.0604	
OR [95%-CI]; p-value	2.67 [0.41, 17.17], 0.2936		11.64 [0.58, 233.43], 0.0575		5.60 [1.11, 28.32], 0.0254	
RD [95%-CI]; p-value	0.20 [-0.15, 0.55], 0.2636		0.36 [0.09, 0.63], 0.0092		0.30 [0.08, 0.52], 0.0074	
Vist 13/ET:n/N1 (%)	7/15 (46.7)	1/10 (10.0)	9/19 (47.4)	0/8 (0.0)	16/34 (47.1)	1/18 (5.6)
RR [95%-CI]; p-value	4.67 [0.67, 32.36], 0.1190		8.05 [0.52, 123.53], 0.1343		8.47 [1.22, 58.82], 0.0307	
OR [95%-CI]; p-value	7.88 [0.79, 78.67], 0.0542		14.40 [0.72, 287.98], 0.0345		15.11 [1.80, 126.68], 0.0024	
RD [95%-CI]; p-value	0.37 [0.05, 0.68], 0.0219		0.41 [0.14, 0.69], 0.0031		0.42 [0.22, 0.61], <0.0001	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
EAP:n/N2 (%)	40/100 (40.0)	3/52 (5.8)	39/100 (39.0)	5/52 (9.6)	79/200 (39.5)	8/104 (7.7)
RR [95%-CI]; p-value	6.93 [2.25, 21.34], 0.0007		4.06 [1.70, 9.67], 0.0016		5.14 [2.58, 10.21], <0.0001	
OR [95%-CI]; p-value	10.89 [3.17, 37.34], <0.0001		6.01 [2.20, 16.43], 0.0002		7.83 [3.61, 17.01], <0.0001	
RD [95%-CI]; p-value	0.34 [0.23, 0.46], <0.0001		0.29 [0.17, 0.42], <0.0001		0.32 [0.23, 0.40], <0.0001	
Vist 13/ET:n/N2 (%)	42/100 (42.0)	5/52 (9.6)	49/100 (49.0)	7/52 (13.5)	91/200 (45.5)	12/104 (11.5)
RR [95%-CI]; p-value	4.37 [1.84, 10.37], 0.0008		3.64 [1.78, 7.46], 0.0004		3.94 [2.27, 6.86], <0.0001	
OR [95%-CI]; p-value	6.81 [2.49, 18.57], <0.0001		6.18 [2.54, 15.00], <0.0001		6.40 [3.30, 12.42], <0.0001	
RD [95%-CI]; p-value	0.32 [0.20, 0.45], <0.0001		0.36 [0.22, 0.49], <0.0001		0.34 [0.25, 0.43], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_1_1_1_m_pth30pct_vitd_pp.sas using SAS 9.4

Table 12.2.1.1.2.s8.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.7347		0.8909		0.8800	
Vist 13/ET	0.1354		0.6499		0.5247	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
EAP:n/N1 (%)	11/15 (73.3)	3/10 (30.0)	13/19 (68.4)	2/8 (25.0)	24/34 (70.6)	5/18 (27.8)
RR [95%-CI]; p-value	2.44 [0.90, 6.61], 0.0782		2.74 [0.79, 9.44], 0.1111		2.54 [1.17, 5.52], 0.0185	
OR [95%-CI]; p-value	6.42 [1.09, 37.73], 0.0325		6.50 [1.00, 42.17], 0.0381		6.24 [1.76, 22.18], 0.0031	
RD [95%-CI]; p-value	0.43 [0.07, 0.79], 0.0188		0.43 [0.07, 0.80], 0.0199		0.43 [0.17, 0.69], 0.0011	
Vist 13/ET:n/N1 (%)	9/15 (60.0)	4/10 (40.0)	15/19 (78.9)	2/8 (25.0)	24/34 (70.6)	6/18 (33.3)
RR [95%-CI]; p-value	1.50 [0.63, 3.56], 0.3578		3.16 [0.93, 10.72], 0.0652		2.12 [1.06, 4.22], 0.0327	
OR [95%-CI]; p-value	2.25 [0.44, 11.52], 0.3268		11.25 [1.61, 78.57], 0.0080		4.80 [1.41, 16.37], 0.0097	
RD [95%-CI]; p-value	0.20 [-0.19, 0.59], 0.3173		0.54 [0.19, 0.89], 0.0026		0.37 [0.11, 0.64], 0.0061	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
EAP:n/N2 (%)	74/100 (74.0)	13/52 (25.0)	72/100 (72.0)	15/52 (28.8)	146/200 (73.0)	28/104 (26.9)
RR [95%-CI]; p-value	2.96 [1.82, 4.81], <0.0001		2.50 [1.60, 3.89], <0.0001		2.71 [1.95, 3.76], <0.0001	
OR [95%-CI]; p-value	8.54 [3.95, 18.45], <0.0001		6.34 [3.02, 13.32], <0.0001		7.34 [4.30, 12.52], <0.0001	
RD [95%-CI]; p-value	0.49 [0.34, 0.64], <0.0001		0.43 [0.28, 0.58], <0.0001		0.46 [0.36, 0.57], <0.0001	
Vist 13/ET:n/N2 (%)	69/100 (69.0)	11/52 (21.2)	72/100 (72.0)	16/52 (30.8)	141/200 (70.5)	27/104 (26.0)
RR [95%-CI]; p-value	3.26 [1.90, 5.60], <0.0001		2.34 [1.53, 3.58], <0.0001		2.72 [1.94, 3.80], <0.0001	
OR [95%-CI]; p-value	8.30 [3.77, 18.26], <0.0001		5.79 [2.78, 12.04], <0.0001		6.82 [4.00, 11.62], <0.0001	
RD [95%-CI]; p-value	0.48 [0.34, 0.62], <0.0001		0.41 [0.26, 0.57], <0.0001		0.45 [0.34, 0.55], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_2_1_1_2_m_pth10pct_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6607		0.9228		0.8641	
Comparison Baseline vs. EAP	0.2840		0.7377		0.2947	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	22.2 (5.36)	18.6 (4.81)	20.8 (5.16)	23.7 (4.46)	21.4 (5.22)	20.9 (5.21)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	66.1 (20.15)	21.1 (7.69)	69.6 (20.80)	27.5 (4.11)	68.0 (20.29)	23.9 (7.00)
EAP						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	63.2 (12.95)	21.7 (7.37)	66.6 (18.13)	26.4 (3.47)	65.1 (15.91)	23.8 (6.27)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	44.8 (4.42)	1.1 (5.49)	48.9 (4.02)	3.7 (6.29)	46.4 (2.93)	3.1 (4.02)
95% CI	[35.58, 53.93]	[-10.28, 12.48]	[40.55, 57.16]	[-9.27, 16.70]	[40.50, 52.29]	[-4.95, 11.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	43.65		45.14		43.26	
95% CI	[28.61, 58.69]		[29.49, 60.78]		[33.24, 53.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.40		2.57		2.58	
95% CI	[1.38, 3.42]		[1.51, 3.62]		[1.83, 3.33]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	41.5 (2.88)	2.3 (3.57)	46.1 (3.28)	1.9 (5.13)	43.4 (2.20)	2.9 (3.01)
95% CI	[35.57, 47.51]	[-5.10, 9.71]	[39.34, 52.89]	[-8.69, 12.50]	[38.96, 47.80]	[-3.14, 8.98]
Diff in LS-Mean [ER-Calcifediol - Placebo]	39.23		44.21		40.46	
95% CI	[29.45, 49.02]		[31.44, 56.97]		[32.96, 47.96]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.39		2.98		3.22	
95% CI	[2.17, 4.60]		[1.85, 4.11]		[2.38, 4.05]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	19.5 (5.02)	19.4 (5.86)	19.4 (5.62)	18.6 (5.52)	19.4 (5.32)	19.0 (5.68)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	68.0 (24.44)	16.7 (5.83)	69.2 (23.03)	18.8 (6.52)	68.6 (23.70)	17.7 (6.23)
EAP						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	67.4 (23.58)	16.9 (5.80)	67.4 (21.47)	18.4 (6.27)	67.4 (22.49)	17.7 (6.06)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.2.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	48.5 (1.93)	-2.7 (2.71)	49.8 (1.91)	-0.3 (2.70)	49.2 (1.36)	-1.5 (1.91)
95% CI	[44.72, 52.36]	[-8.09, 2.61]	[46.02, 53.57]	[-5.65, 5.03]	[46.48, 51.83]	[-5.26, 2.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	51.28		50.10		50.65	
95% CI	[44.71, 57.85]		[43.56, 56.65]		[46.02, 55.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.65		2.62		2.65	
95% CI	[2.20, 3.10]		[2.17, 3.08]		[2.33, 2.97]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.9 (1.88)	-2.4 (2.60)	48.1 (1.73)	-0.2 (2.40)	48.0 (1.27)	-1.3 (1.77)
95% CI	[44.16, 51.58]	[-7.57, 2.70]	[44.65, 51.49]	[-4.99, 4.50]	[45.45, 50.47]	[-4.80, 2.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	50.30		48.32		49.28	
95% CI	[43.97, 56.64]		[42.46, 54.17]		[44.99, 53.57]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.68		2.78		2.74	
95% CI	[2.23, 3.13]		[2.32, 3.23]		[2.42, 3.06]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_2_1_m_25d_vitd_pp.sas using SAS 9.4

Table 12.3.1.1.s8.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.0500		0.0714		0.0047	
Vist 13/ET	0.0515		0.0089		0.0010	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
EAP:n/N1 (%)	15/15 (100.0)	2/10 (20.0)	18/19 (94.7)	2/8 (25.0)	33/34 (97.1)	4/18 (22.2)
RR [95%-CI]; p-value	4.84 [1.40, 16.77], 0.0129		3.79 [1.14, 12.64], 0.0302		4.37 [1.84, 10.39], 0.0009	
OR [95%-CI]; p-value	120.00 [4.82, 2990.12], <0.0001		54.00 [4.12, 707.06], 0.0002		115.50 [11.83, 1127.78], <0.0001	
RD [95%-CI]; p-value	0.77 [0.50, 1.00], <0.0001		0.70 [0.38, 1.00], <0.0001		0.75 [0.55, 0.95], <0.0001	
Vist 13/ET:n/N1 (%)	14/15 (93.3)	2/10 (20.0)	18/19 (94.7)	3/8 (37.5)	32/34 (94.1)	5/18 (27.8)
RR [95%-CI]; p-value	4.67 [1.34, 16.24], 0.0155		2.53 [1.03, 6.22], 0.0438		3.39 [1.60, 7.17], 0.0014	
OR [95%-CI]; p-value	56.00 [4.36, 719.20], 0.0002		30.00 [2.54, 354.87], 0.0011		41.60 [7.14, 242.28], <0.0001	
RD [95%-CI]; p-value	0.73 [0.46, 1.00], <0.0001		0.57 [0.22, 0.92], 0.0014		0.66 [0.44, 0.88], <0.0001	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
EAP:n/N2 (%)	95/100 (95.0)	0/52 (0.0)	98/100 (98.0)	3/52 (5.8)	193/200 (96.5)	3/104 (2.9)
RR [95%-CI]; p-value	99.75 [6.32, 1574.37], 0.0011		16.99 [5.66, 50.97], <0.0001		33.45 [10.96, 102.06], <0.0001	
OR [95%-CI]; p-value	1976.00 [105.86, 36883.55], <0.0001		800.33 [129.45, 4948.25], <0.0001		928.24 [234.99, 3666.69], <0.0001	
RD [95%-CI]; p-value	0.94 [0.89, 0.99], <0.0001		0.92 [0.85, 0.99], <0.0001		0.94 [0.90, 0.98], <0.0001	
Vist 13/ET:n/N2 (%)	90/100 (90.0)	0/52 (0.0)	97/100 (97.0)	3/52 (5.8)	187/200 (93.5)	3/104 (2.9)
RR [95%-CI]; p-value	94.50 [5.98, 1492.12], 0.0012		16.81 [5.60, 50.46], <0.0001		32.41 [10.62, 98.92], <0.0001	
OR [95%-CI]; p-value	936.00 [53.57, 16355.48], <0.0001		528.11 [102.78, 2713.69], <0.0001		484.28 [134.85, 1739.18], <0.0001	
RD [95%-CI]; p-value	0.89 [0.83, 0.95], <0.0001		0.91 [0.84, 0.98], <0.0001		0.91 [0.86, 0.95], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_3_1_1_m_25d30_vitd_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3926		0.0994		0.4801	
Comparison Baseline vs. EAP	0.2420		0.0833		0.5648	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	145.7 (46.95)	137.2 (44.69)	160.3 (78.17)	160.8 (57.61)	153.0 (64.75)	148.1 (52.01)
Visit 13/ET						
n/N1	57/58	34/35	58/59	28/30	115/117	62/65
Mean (SD)	114.7 (65.26)	153.2 (71.44)	127.7 (116.10)	168.6 (69.67)	121.3 (94.21)	160.2 (70.49)
EAP						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	108.6 (51.37)	151.2 (71.50)	130.2 (100.53)	159.4 (62.15)	119.5 (80.42)	155.0 (66.95)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-31.0 (6.58)	19.2 (8.53)	-33.5 (9.56)	6.8 (13.76)	-32.2 (5.76)	13.0 (7.88)
95% CI	[-44.03, -17.89]	[2.21, 36.12]	[-52.53, -14.50]	[-20.56, 34.18]	[-43.60, -20.86]	[-2.59, 28.52]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-50.12		-40.32		-45.20	
95% CI	[-71.60, -28.65]		[-73.65, -7.00]		[-64.47, -25.92]	
p-value	<0.0001		0.0183		<0.0001	
Hedges' g	-1.00		-0.55		-0.74	
95% CI	[-1.45, -0.56]		[-1.01, -0.10]		[-1.06, -0.42]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-36.8 (5.47)	13.7 (7.04)	-30.1 (7.47)	-1.4 (10.47)	-33.5 (4.60)	6.2 (6.19)
95% CI	[-47.69, -25.97]	[-0.29, 27.69]	[-44.92, -15.22]	[-22.21, 19.43]	[-42.55, -24.38]	[-6.01, 18.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-50.53		-28.68		-39.68	
95% CI	[-68.27, -32.78]		[-54.25, -3.10]		[-54.92, -24.45]	
p-value	<0.0001		0.0284		<0.0001	
Hedges' g	-1.22		-0.50		-0.81	
95% CI	[-1.67, -0.77]		[-0.94, -0.06]		[-1.12, -0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	143.2 (56.81)	136.6 (37.40)	125.8 (34.18)	147.1 (60.26)	134.3 (47.20)	142.1 (50.57)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	111.8 (58.52)	143.0 (60.98)	94.3 (42.60)	164.3 (82.39)	102.9 (51.57)	154.2 (73.19)
EAP						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	110.3 (51.86)	140.4 (59.29)	98.0 (39.89)	157.0 (68.41)	104.0 (46.32)	149.2 (64.23)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for PTH Intact (pg/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-30.6 (6.50)	4.9 (9.45)	-31.9 (5.73)	18.8 (8.10)	-31.8 (4.32)	13.1 (6.18)
95% CI	[-43.55, -17.68]	[-13.86, 23.74]	[-43.24, -20.47]	[2.67, 34.87]	[-40.34, -23.26]	[0.86, 25.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-35.56		-50.62		-44.86	
95% CI	[-58.40, -12.72]		[-70.57, -30.67]		[-59.78, -29.95]	
p-value	0.0027		<0.0001		<0.0001	
Hedges' g	-0.72		-1.10		-0.91	
95% CI	[-1.19, -0.26]		[-1.56, -0.63]		[-1.24, -0.58]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-32.2 (5.44)	2.5 (7.91)	-28.9 (4.53)	12.1 (6.46)	-30.9 (3.52)	8.1 (5.05)
95% CI	[-43.05, -21.38]	[-13.23, 18.27]	[-37.89, -19.90]	[-0.69, 24.98]	[-37.82, -23.94]	[-1.87, 18.06]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-34.74		-41.04		-38.98	
95% CI	[-53.86, -15.61]		[-56.89, -25.19]		[-51.14, -26.82]	
p-value	0.0005		<0.0001		<0.0001	
Hedges' g	-0.83		-1.06		-0.94	
95% CI	[-1.30, -0.36]		[-1.52, -0.60]		[-1.27, -0.61]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; iPTH: Parathyroid Hormone intact; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_2_1_m_pth_bl25d_pp.sas using SAS 9.4

Table 12.2.1.1.1.s9.pp
Number (n, %) of Subjects with a Mean Reduction of ≥30% in Plasma iPTH
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.4173		0.1002		0.2816	
Vist 13/ET	0.2537		0.2363		0.9393	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
EAP:n/N1 (%)	24/58 (41.4)	2/35 (5.7)	22/59 (37.3)	5/30 (16.7)	46/117 (39.3)	7/65 (10.8)
RR [95%-CI]; p-value	7.24 [1.82, 28.79], 0.0049		2.24 [0.94, 5.32], 0.0683		3.65 [1.75, 7.61], 0.0006	
OR [95%-CI]; p-value	11.65 [2.55, 53.25], 0.0002		2.97 [0.99, 8.89], 0.0455		5.37 [2.25, 12.78], <0.0001	
RD [95%-CI]; p-value	0.36 [0.21, 0.50], <0.0001		0.21 [0.02, 0.39], 0.0261		0.29 [0.17, 0.40], <0.0001	
Vist 13/ET:n/N1 (%)	25/58 (43.1)	2/35 (5.7)	28/59 (47.5)	5/30 (16.7)	53/117 (45.3)	7/65 (10.8)
RR [95%-CI]; p-value	7.54 [1.90, 29.92], 0.0040		2.85 [1.22, 6.62], 0.0151		4.21 [2.03, 8.71], 0.0001	
OR [95%-CI]; p-value	12.50 [2.74, 57.09], 0.0001		4.52 [1.52, 13.40], 0.0045		6.86 [2.89, 16.29], <0.0001	
RD [95%-CI]; p-value	0.37 [0.23, 0.52], <0.0001		0.31 [0.12, 0.49], 0.0011		0.35 [0.23, 0.46], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
EAP:n/N2 (%)	22/57 (38.6)	3/27 (11.1)	25/60 (41.7)	0/30 (0.0)	47/117 (40.2)	3/57 (5.3)
RR [95%-CI]; p-value	3.47 [1.14, 10.60], 0.0287		25.42 [1.60, 403.69], 0.0218		7.63 [2.48, 23.47], 0.0004	
OR [95%-CI]; p-value	5.03 [1.35, 18.70], 0.0101		42.86 [2.50, 734.67], <0.0001		12.09 [3.57, 40.93], <0.0001	
RD [95%-CI]; p-value	0.27 [0.10, 0.45], 0.0019		0.40 [0.27, 0.53], <0.0001		0.35 [0.24, 0.46], <0.0001	
Vist 13/ET:n/N2 (%)	24/57 (42.1)	4/27 (14.8)	30/60 (50.0)	2/30 (6.7)	54/117 (46.2)	6/57 (10.5)
RR [95%-CI]; p-value	2.84 [1.09, 7.38], 0.0319		7.50 [1.92, 29.30], 0.0038		4.38 [2.01, 9.58], 0.0002	
OR [95%-CI]; p-value	4.18 [1.28, 13.68], 0.0132		14.00 [3.06, 64.09], <0.0001		7.29 [2.90, 18.29], <0.0001	
RD [95%-CI]; p-value	0.27 [0.09, 0.46], 0.0039		0.43 [0.28, 0.59], <0.0001		0.36 [0.24, 0.48], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_1_1_1_m_pth30pct_bl25d_pp.sas using SAS 9.4

Table 12.2.1.1.2.s9.pp
Number (n, %) of Subjects with a Mean Reduction of ≥10% in Plasma iPTH
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.5492		0.6102		0.9494	
Vist 13/ET	0.2124		0.8987		0.4152	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
EAP:n/N1 (%)	43/58 (74.1)	8/35 (22.9)	45/59 (76.3)	10/30 (33.3)	88/117 (75.2)	18/65 (27.7)
RR [95%-CI]; p-value	3.24 [1.73, 6.07], 0.0002		2.29 [1.35, 3.87], 0.0020		2.72 [1.81, 4.08], <0.0001	
OR [95%-CI]; p-value	9.68 [3.62, 25.88], <0.0001		6.43 [2.44, 16.92], <0.0001		7.92 [3.99, 15.74], <0.0001	
RD [95%-CI]; p-value	0.51 [0.33, 0.69], <0.0001		0.43 [0.23, 0.63], <0.0001		0.48 [0.34, 0.61], <0.0001	
Vist 13/ET:n/N1 (%)	38/58 (65.5)	6/35 (17.1)	42/59 (71.2)	9/30 (30.0)	80/117 (68.4)	15/65 (23.1)
RR [95%-CI]; p-value	3.82 [1.80, 8.11], 0.0005		2.37 [1.34, 4.20], 0.0030		2.96 [1.87, 4.70], <0.0001	
OR [95%-CI]; p-value	9.18 [3.27, 25.79], <0.0001		5.76 [2.20, 15.10], 0.0002		7.21 [3.59, 14.46], <0.0001	
RD [95%-CI]; p-value	0.48 [0.31, 0.66], <0.0001		0.41 [0.21, 0.61], <0.0001		0.45 [0.32, 0.59], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
EAP:n/N2 (%)	42/57 (73.7)	8/27 (29.6)	40/60 (66.7)	7/30 (23.3)	82/117 (70.1)	15/57 (26.3)
RR [95%-CI]; p-value	2.49 [1.36, 4.54], 0.0030		2.86 [1.46, 5.60], 0.0022		2.66 [1.70, 4.18], <0.0001	
OR [95%-CI]; p-value	6.65 [2.41, 18.35], 0.0001		6.57 [2.41, 17.90], 0.0001		6.56 [3.23, 13.34], <0.0001	
RD [95%-CI]; p-value	0.44 [0.23, 0.65], <0.0001		0.43 [0.24, 0.63], <0.0001		0.44 [0.30, 0.58], <0.0001	
Vist 13/ET:n/N2 (%)	40/57 (70.2)	9/27 (33.3)	45/60 (75.0)	9/30 (30.0)	85/117 (72.6)	18/57 (31.6)
RR [95%-CI]; p-value	2.11 [1.20, 3.68], 0.0091		2.50 [1.42, 4.40], 0.0015		2.30 [1.55, 3.43], <0.0001	
OR [95%-CI]; p-value	4.71 [1.76, 12.55], 0.0014		7.00 [2.64, 18.56], <0.0001		5.76 [2.88, 11.48], <0.0001	
RD [95%-CI]; p-value	0.37 [0.15, 0.58], 0.0007		0.45 [0.25, 0.65], <0.0001		0.41 [0.27, 0.56], <0.0001	

Abbreviations: CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; iPTH: intact parathyroid hormone; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_2_1_1_2_m_pth10pct_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1498		0.0257		0.0103	
Comparison Baseline vs. EAP	0.0924		0.3727		0.0645	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	15.4 (2.58)	15.1 (3.09)	15.0 (3.27)	14.8 (3.25)	15.2 (2.95)	14.9 (3.14)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	61.9 (25.22)	14.2 (4.89)	65.4 (25.88)	16.4 (6.22)	63.7 (25.50)	15.2 (5.58)
EAP						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	62.3 (25.00)	14.4 (4.95)	62.3 (21.36)	15.9 (5.42)	62.3 (23.14)	15.1 (5.18)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	46.5 (2.66)	-0.8 (3.47)	50.4 (2.86)	1.4 (4.19)	48.5 (1.94)	0.2 (2.70)
95% CI	[41.20, 51.76]	[-7.75, 6.05]	[44.71, 56.08]	[-6.92, 9.74]	[44.62, 52.29]	[-5.07, 5.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.33		48.98		48.20	
95% CI	[38.63, 56.02]		[38.89, 59.07]		[41.64, 54.76]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.34		2.24		2.31	
95% CI	[1.80, 2.87]		[1.67, 2.80]		[1.92, 2.70]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	46.9 (2.61)	-0.6 (3.36)	47.3 (2.30)	1.1 (3.22)	47.1 (1.73)	0.2 (2.33)
95% CI	[41.70, 52.05]	[-7.28, 6.05]	[42.76, 51.90]	[-5.34, 7.47]	[43.69, 50.53]	[-4.39, 4.82]
Diff in LS-Mean [ER-Calcifediol - Placebo]	47.48		46.26		46.89	
95% CI	[39.04, 55.93]		[38.39, 54.13]		[41.15, 52.64]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.39		2.61		2.51	
95% CI	[1.85, 2.93]		[2.03, 3.19]		[2.12, 2.91]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	24.3 (2.46)	24.6 (3.14)	24.2 (2.89)	23.8 (3.42)	24.3 (2.68)	24.2 (3.29)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	73.7 (20.96)	21.4 (5.58)	73.0 (18.27)	23.2 (5.94)	73.4 (19.56)	22.4 (5.79)
EAP						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	71.4 (18.73)	22.0 (5.21)	72.2 (19.38)	23.2 (5.49)	71.8 (18.99)	22.6 (5.35)

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.2.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum 25D (ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	49.3 (2.34)	-3.1 (3.41)	48.9 (1.99)	-0.7 (2.79)	49.1 (1.53)	-1.9 (2.18)
95% CI	[44.67, 54.00]	[-9.83, 3.73]	[44.90, 52.82]	[-6.25, 4.86]	[46.10, 52.13]	[-6.21, 2.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	52.39		49.55		51.01	
95% CI	[44.16, 60.62]		[42.73, 56.38]		[45.76, 56.27]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	2.95		3.21		3.09	
95% CI	[2.31, 3.58]		[2.57, 3.85]		[2.64, 3.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	47.0 (2.10)	-2.6 (3.05)	48.1 (2.09)	-0.7 (2.95)	47.5 (1.47)	-1.7 (2.12)
95% CI	[42.82, 51.16]	[-8.62, 3.50]	[43.91, 52.21]	[-6.61, 5.14]	[44.63, 50.45]	[-5.84, 2.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	49.55		48.80		49.21	
95% CI	[42.19, 56.91]		[41.60, 55.99]		[44.12, 54.30]	
p-value	<0.0001		<0.0001		<0.0001	
Hedges' g	3.12		2.99		3.08	
95% CI	[2.46, 3.77]		[2.38, 3.61]		[2.63, 3.53]	

Abbreviations: 25 D: 25-Hydroxyvitamin D; ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_2_1_m_25d_bl25d_pp.sas using SAS 9.4

Table 12.3.1.1.s9.pp
Number (n, %) of Subjects with Adequate Serum 25D Levels (≥30 ng/mL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
EAP	0.8982		0.2085		0.2236	
Vist 13/ET	0.3161		0.1395		0.0561	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
EAP:n/N1 (%)	53/58 (91.4)	1/35 (2.9)	57/59 (96.6)	1/30 (3.3)	110/117 (94.0)	2/65 (3.1)
RR [95%-CI]; p-value	31.98 [4.63, 221.09], 0.0004		28.98 [4.22, 199.20], 0.0006		30.56 [7.80, 119.67], <0.0001	
OR [95%-CI]; p-value	360.40 [40.34, 3219.60], <0.0001		826.50 [71.91, 9498.89], <0.0001		495.00 [99.77, 2455.90], <0.0001	
RD [95%-CI]; p-value	0.89 [0.79, 0.98], <0.0001		0.93 [0.85, 1.00], <0.0001		0.91 [0.85, 0.97], <0.0001	
Vist 13/ET:n/N1 (%)	50/58 (86.2)	0/35 (0.0)	56/59 (94.9)	1/30 (3.3)	106/117 (90.6)	1/65 (1.5)
RR [95%-CI]; p-value	61.21 [3.90, 961.41], 0.0034		28.47 [4.14, 195.77], 0.0007		58.89 [8.41, 412.14], <0.0001	
OR [95%-CI]; p-value	437.50 [24.32, 7868.78], <0.0001		541.33 [53.89, 5438.18], <0.0001		616.73 [77.78, 4889.87], <0.0001	
RD [95%-CI]; p-value	0.85 [0.75, 0.94], <0.0001		0.92 [0.83, 1.00], <0.0001		0.89 [0.83, 0.95], <0.0001	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
EAP:n/N2 (%)	57/57 (100.0)	1/27 (3.7)	59/60 (98.3)	4/30 (13.3)	116/117 (99.1)	5/57 (8.8)
RR [95%-CI]; p-value	26.77 [3.91, 183.20], 0.0008		7.38 [2.96, 18.38], <0.0001		11.30 [4.89, 26.11], <0.0001	
OR [95%-CI]; p-value	2964.00 [96.35, 91180.21], <0.0001		383.50 [40.85, 3600.00], <0.0001		1206.40 [137.50, 10585.09], <0.0001	
RD [95%-CI]; p-value	0.95 [0.88, 1.00], <0.0001		0.85 [0.72, 0.98], <0.0001		0.90 [0.83, 0.98], <0.0001	
Vist 13/ET:n/N2 (%)	54/57 (94.7)	2/27 (7.4)	59/60 (98.3)	5/30 (16.7)	113/117 (96.6)	7/57 (12.3)
RR [95%-CI]; p-value	12.79 [3.37, 48.60], 0.0002		5.90 [2.65, 13.14], <0.0001		7.86 [3.93, 15.75], <0.0001	
OR [95%-CI]; p-value	225.00 [35.34, 1432.32], <0.0001		295.00 [32.77, 2655.44], <0.0001		201.79 [56.51, 720.53], <0.0001	
RD [95%-CI]; p-value	0.87 [0.76, 0.99], <0.0001		0.82 [0.68, 0.95], <0.0001		0.84 [0.75, 0.93], <0.0001	

Abbreviations: 25D: 25-Hydroxyvitamin D; CI: Confidence Interval; EAP: efficacy assessment phase; ER: Extended Release; ET: End of Treatment; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_3_1_1_m_25d30_bl25d_pp.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalysen - Sicherheitsendpunkte Sicherheits-relevante sHPT-assoziierte Parameter (ITT-Population)

Folgende Daten werden für die ITT-Population

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum
- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.12.1.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7108		0.3837		0.7849	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	9.2 (0.30)	9.3 (0.26)	9.2 (0.36)	9.2 (0.32)	9.2 (0.33)	9.2 (0.29)
Visit 13/ET						
n/N1	57/59	30/30	47/50	28/32	104/109	58/62
Mean (SD)	9.5 (0.45)	9.3 (0.37)	9.5 (0.46)	9.4 (0.52)	9.5 (0.45)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.15, 0.36]	[-0.08, 0.20]	[0.19, 0.39]	[0.04, 0.30]	[0.20, 0.35]	[0.01, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.12		0.17	
95% CI	[0.02, 0.37]		[-0.04, 0.29]		[0.05, 0.29]	
p-value	0.0259		0.1405		0.0064	
Hedges' g	0.54		0.36		0.46	
95% CI	[0.09, 0.99]		[-0.11, 0.82]		[0.13, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_m_dca_age.sas using SAS 9.4

Table 12.4.12.1.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	9.2 (0.28)	9.2 (0.29)	9.3 (0.34)	9.3 (0.24)	9.2 (0.31)	9.3 (0.27)
Visit 13/ET						
n/N2	74/82	38/42	85/94	34/40	159/176	72/82
Mean (SD)	9.5 (0.54)	9.4 (0.28)	9.5 (0.37)	9.4 (0.57)	9.5 (0.46)	9.4 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.2 (0.06)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.23, 0.42]	[0.03, 0.28]	[0.20, 0.35]	[-0.07, 0.17]	[0.24, 0.36]	[0.02, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.22		0.19	
95% CI	[0.01, 0.33]		[0.08, 0.37]		[0.09, 0.30]	
p-value	0.0376		0.0029		0.0004	
Hedges' g	0.43		0.63		0.52	
95% CI	[0.04, 0.82]		[0.23, 1.03]		[0.23, 0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_m_dca_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3875		0.3834		0.9660	
Comparison Baseline vs. EAP	0.9715		0.4617		0.5618	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	50/50	32/32	109/109	62/62
Mean (SD)	3.8 (0.53)	4.0 (0.57)	3.9 (0.62)	3.8 (0.55)	3.8 (0.57)	3.9 (0.57)
Visit 13/ET						
n/N1	57/59	30/30	47/50	28/32	104/109	58/62
Mean (SD)	3.9 (0.67)	4.0 (0.70)	4.2 (0.92)	3.7 (0.88)	4.0 (0.80)	3.9 (0.81)
EAP						
n/N1	57/59	30/30	48/50	29/32	105/109	59/62
Mean (SD)	3.9 (0.55)	4.1 (0.53)	4.1 (0.80)	3.7 (0.65)	4.0 (0.68)	3.9 (0.61)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.11)	0.3 (0.11)	-0.0 (0.14)	0.2 (0.07)	0.0 (0.09)
95% CI	[-0.09, 0.22]	[-0.13, 0.30]	[0.11, 0.55]	[-0.32, 0.26]	[0.07, 0.33]	[-0.16, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.36		0.19	
95% CI	[-0.29, 0.24]		[-0.01, 0.73]		[-0.03, 0.40]	
p-value	0.8692		0.0534		0.0956	
Hedges' g	0.09		0.43		0.26	
95% CI	[-0.35, 0.52]		[-0.04, 0.90]		[-0.06, 0.58]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.1 (0.08)	0.3 (0.09)	-0.0 (0.11)	0.2 (0.05)	0.0 (0.07)
95% CI	[-0.00, 0.22]	[-0.04, 0.26]	[0.09, 0.44]	[-0.23, 0.22]	[0.09, 0.29]	[-0.09, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		0.28		0.15	
95% CI	[-0.19, 0.19]		[-0.01, 0.56]		[-0.02, 0.31]	
p-value	0.9976		0.0580		0.0795	
Hedges' g	0.16		0.38		0.28	
95% CI	[-0.28, 0.60]		[-0.08, 0.84]		[-0.04, 0.60]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	3.7 (0.55)	3.7 (0.57)	3.7 (0.53)	3.6 (0.39)	3.7 (0.54)	3.7 (0.49)
Visit 13/ET						
n/N2	74/82	38/42	85/94	34/40	159/176	72/82
Mean (SD)	3.9 (0.73)	3.8 (0.61)	3.9 (0.61)	3.7 (0.54)	3.9 (0.67)	3.8 (0.57)
EAP						
n/N2	74/82	39/42	88/94	36/40	162/176	75/82
Mean (SD)	3.9 (0.68)	3.8 (0.60)	3.9 (0.60)	3.8 (0.41)	3.9 (0.64)	3.8 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.4.14.1.s1
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.07)	0.1 (0.09)	0.2 (0.05)	0.1 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.16, 0.41]	[-0.09, 0.27]	[0.09, 0.30]	[-0.08, 0.25]	[0.16, 0.32]	[-0.04, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.11		0.15	
95% CI	[-0.02, 0.42]		[-0.09, 0.31]		[0.01, 0.30]	
p-value	0.0789		0.2703		0.0425	
Hedges' g	0.34		0.16		0.25	
95% CI	[-0.05, 0.74]		[-0.24, 0.55]		[-0.03, 0.53]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.04)	0.1 (0.07)	0.2 (0.03)	0.1 (0.05)
95% CI	[0.11, 0.31]	[0.00, 0.28]	[0.13, 0.30]	[-0.01, 0.26]	[0.15, 0.28]	[0.04, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.06		0.09		0.07	
95% CI	[-0.11, 0.24]		[-0.07, 0.25]		[-0.04, 0.19]	
p-value	0.4691		0.2637		0.2130	
Hedges' g	0.15		0.16		0.16	
95% CI	[-0.23, 0.54]		[-0.23, 0.54]		[-0.12, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_14_1_m_phos_age.sas using SAS 9.4

Table 12.5.1.1.1.s1
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8407		0.9975		0.9293	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	38/59	17/30	31/50	22/32	69/109	39/62
Mean (SD)	44.7 (34.47)	35.7 (19.86)	37.6 (29.38)	37.3 (32.34)	41.5 (32.25)	36.6 (27.29)
Visit 13/ET						
n/N1	33/59	13/30	30/50	15/32	63/109	28/62
Mean (SD)	49.5 (41.83)	54.7 (79.42)	72.4 (87.66)	62.6 (58.37)	60.4 (68.06)	58.9 (67.72)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	11.8 (10.21)	10.5 (16.31)	41.6 (19.99)	22.5 (27.62)	26.3 (10.66)	17.5 (15.75)
95% CI	[-8.86, 32.54]	[-22.56, 43.58]	[0.69, 82.46]	[-33.98, 79.00]	[5.06, 47.63]	[-13.94, 48.97]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.33		19.07		8.83	
95% CI	[-37.74, 40.39]		[-50.67, 88.80]		[-29.16, 46.82]	
p-value	0.9455		0.5803		0.6442	
Hedges' g	0.03		0.18		0.10	
95% CI	[-0.65, 0.72]		[-0.53, 0.90]		[-0.39, 0.60]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_5_1_1_m_fgf23_age.sas using SAS 9.4

Table 12.5.1.1.1.s1
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	59/82	24/42	53/94	25/40	112/176	49/82
Mean (SD)	48.8 (59.35)	51.2 (41.99)	33.3 (21.67)	34.4 (28.12)	41.5 (46.06)	42.6 (36.23)
Visit 13/ET						
n/N2	44/82	13/42	45/94	13/40	89/176	26/82
Mean (SD)	52.8 (54.95)	53.6 (29.37)	52.5 (51.22)	61.5 (55.49)	52.6 (52.79)	57.6 (43.69)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	4.0 (8.09)	2.6 (14.39)	25.4 (9.76)	20.3 (15.69)	13.6 (6.31)	12.4 (10.60)
95% CI	[-12.24, 20.25]	[-26.31, 31.47]	[5.74, 45.11]	[-11.32, 51.97]	[1.12, 26.18]	[-8.63, 33.45]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.42		5.10		1.24	
95% CI	[-31.75, 34.59]		[-32.48, 42.68]		[-23.30, 25.78]	
p-value	0.9317		0.7856		0.9206	
Hedges' g	0.13		0.18		0.13	
95% CI	[-0.49, 0.74]		[-0.45, 0.82]		[-0.31, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_5_1_1_m_fgf23_age.sas using SAS 9.4

Table 12.4.12.1.2.s1
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5198		0.8698		0.7350	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	59/59	30/30	49/50	32/32	108/109	62/62
Mean (SD)	29.1 (12.94)	31.2 (10.57)	30.1 (10.80)	31.1 (10.23)	29.5 (11.97)	31.1 (10.31)
Visit 13/ET						
n/N1	57/59	30/30	47/50	28/32	104/109	58/62
Mean (SD)	28.9 (12.41)	31.1 (12.07)	29.4 (13.58)	30.0 (10.92)	29.2 (12.89)	30.6 (11.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.7 (0.89)	0.0 (1.23)	-0.6 (1.04)	-0.7 (1.34)	-0.6 (0.68)	-0.3 (0.91)
95% CI	[-2.49, 1.06]	[-2.42, 2.47]	[-2.62, 1.52]	[-3.36, 2.00]	[-1.98, 0.72]	[-2.14, 1.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.74		0.13		-0.29	
95% CI	[-3.77, 2.28]		[-3.25, 3.52]		[-2.55, 1.96]	
p-value	0.6257		0.9383		0.7988	
Hedges' g	-0.07		0.02		-0.03	
95% CI	[-0.51, 0.37]		[-0.45, 0.48]		[-0.35, 0.29]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_2_m_egfr_age.sas using SAS 9.4

Table 12.4.12.1.2.s1
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	82/82	42/42	94/94	40/40	176/176	82/82
Mean (SD)	31.2 (9.49)	33.1 (11.39)	31.4 (9.47)	32.3 (9.18)	31.3 (9.45)	32.7 (10.31)
Visit 13/ET						
n/N2	74/82	38/42	85/94	34/40	159/176	72/82
Mean (SD)	30.5 (11.43)	32.7 (10.83)	29.5 (10.28)	30.6 (10.43)	29.9 (10.81)	31.8 (10.62)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.3 (0.85)	-0.7 (1.20)	-1.8 (0.57)	-1.6 (0.90)	-1.0 (0.51)	-1.2 (0.75)
95% CI	[-1.94, 1.44]	[-3.07, 1.67]	[-2.97, -0.71]	[-3.40, 0.18]	[-2.02, -0.03]	[-2.67, 0.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.45		-0.23		0.16	
95% CI	[-2.48, 3.37]		[-2.34, 1.89]		[-1.63, 1.95]	
p-value	0.7625		0.8332		0.8610	
Hedges' g	0.12		-0.03		0.04	
95% CI	[-0.27, 0.51]		[-0.43, 0.36]		[-0.23, 0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_12_1_2_m_egfr_age.sas using SAS 9.4

Table 12.4.15.1.1.s1
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0364		0.1948		0.0218	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
Baseline						
n/N1	49/59	24/30	42/50	26/32	91/109	50/62
Mean (SD)	0.6 (0.68)	0.7 (0.68)	0.8 (1.04)	1.2 (1.45)	0.7 (0.87)	1.0 (1.16)
Visit 13/ET						
n/N1	48/59	26/30	40/50	22/32	88/109	48/62
Mean (SD)	0.5 (0.54)	0.8 (0.98)	0.9 (1.11)	1.2 (2.14)	0.7 (0.86)	1.0 (1.61)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.08)	0.2 (0.11)	0.1 (0.18)	0.3 (0.24)	-0.0 (0.09)	0.2 (0.13)
95% CI	[-0.25, 0.07]	[-0.06, 0.37]	[-0.29, 0.45]	[-0.14, 0.84]	[-0.19, 0.18]	[-0.00, 0.50]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.24		-0.27		-0.25	
95% CI	[-0.51, 0.02]		[-0.88, 0.34]		[-0.56, 0.06]	
p-value	0.0725		0.3845		0.1183	
Hedges' g	-0.38		-0.23		-0.28	
95% CI	[-0.85, 0.10]		[-0.75, 0.29]		[-0.63, 0.08]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_15_1_1_m_ua_age.sas using SAS 9.4

Table 12.4.15.1.1.s1
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Age≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
Baseline						
n/N2	67/82	38/42	68/94	29/40	135/176	67/82
Mean (SD)	0.6 (0.82)	0.6 (1.02)	0.7 (1.03)	0.6 (0.88)	0.7 (0.93)	0.6 (0.95)
Visit 13/ET						
n/N2	57/82	34/42	57/94	21/40	114/176	55/82
Mean (SD)	0.9 (1.39)	0.5 (0.76)	0.9 (1.45)	0.6 (0.78)	0.9 (1.41)	0.5 (0.76)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.11)	-0.1 (0.15)	0.2 (0.11)	-0.0 (0.18)	0.2 (0.08)	-0.1 (0.12)
95% CI	[-0.02, 0.42]	[-0.36, 0.22]	[-0.05, 0.39]	[-0.40, 0.33]	[0.03, 0.34]	[-0.28, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.27		0.20		0.24	
95% CI	[-0.10, 0.64]		[-0.22, 0.63]		[-0.04, 0.52]	
p-value	0.1454		0.3437		0.0955	
Hedges' g	0.31		0.25		0.29	
95% CI	[-0.12, 0.74]		[-0.26, 0.76]		[-0.04, 0.61]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_15_1_1_m_ua_age.sas using SAS 9.4

Table 12.4.12.1.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8698		0.3710		0.4986	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	9.2 (0.29)	9.2 (0.24)	9.3 (0.33)	9.3 (0.26)	9.3 (0.32)	9.3 (0.25)
Visit 13/ET						
n/N1	66/71	32/33	65/71	32/39	131/142	64/72
Mean (SD)	9.5 (0.47)	9.4 (0.34)	9.6 (0.37)	9.5 (0.59)	9.6 (0.43)	9.4 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.05)	0.1 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.20, 0.38]	[0.00, 0.26]	[0.19, 0.38]	[0.00, 0.27]	[0.22, 0.35]	[0.04, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.16		0.15		0.15	
95% CI	[0.01, 0.32]		[-0.02, 0.31]		[0.04, 0.26]	
p-value	0.0428		0.0781		0.0074	
Hedges' g	0.45		0.38		0.42	
95% CI	[0.03, 0.87]		[-0.04, 0.80]		[0.12, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_1_m_dca_sex.sas using SAS 9.4

Table 12.4.12.1.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	9.2 (0.28)	9.2 (0.31)	9.2 (0.34)	9.2 (0.29)	9.2 (0.31)	9.2 (0.30)
Visit 13/ET						
n/N2	65/70	36/39	67/73	30/33	132/143	66/72
Mean (SD)	9.5 (0.53)	9.3 (0.30)	9.4 (0.41)	9.2 (0.45)	9.4 (0.47)	9.3 (0.38)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.19, 0.40]	[-0.04, 0.24]	[0.20, 0.36]	[-0.06, 0.18]	[0.23, 0.36]	[-0.01, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.22		0.21	
95% CI	[0.02, 0.37]		[0.08, 0.37]		[0.10, 0.32]	
p-value	0.0304		0.0032		0.0003	
Hedges' g	0.50		0.66		0.56	
95% CI	[0.09, 0.91]		[0.22, 1.09]		[0.26, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_1_m_dca_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0292		0.1518		0.6219	
Comparison Baseline vs. EAP	0.1144		0.2284		0.8782	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	71/71	39/39	142/142	72/72
Mean (SD)	3.8 (0.54)	3.9 (0.60)	3.8 (0.42)	3.8 (0.44)	3.8 (0.48)	3.8 (0.52)
Visit 13/ET						
n/N1	66/71	32/33	65/71	32/39	131/142	64/72
Mean (SD)	4.0 (0.66)	3.8 (0.61)	4.0 (0.57)	3.9 (0.72)	4.0 (0.62)	3.8 (0.66)
EAP						
n/N1	66/71	33/33	68/71	33/39	134/142	66/72
Mean (SD)	4.0 (0.62)	4.0 (0.56)	4.0 (0.47)	3.9 (0.55)	4.0 (0.55)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	-0.0 (0.09)	0.1 (0.07)	0.1 (0.09)	0.2 (0.04)	0.0 (0.06)
95% CI	[0.12, 0.37]	[-0.22, 0.13]	[0.01, 0.26]	[-0.09, 0.28]	[0.10, 0.28]	[-0.10, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.29		0.04		0.17	
95% CI	[0.08, 0.51]		[-0.19, 0.26]		[0.01, 0.32]	
p-value	0.0079		0.7374		0.0335	
Hedges' g	0.61		0.04		0.32	
95% CI	[0.18, 1.04]		[-0.38, 0.46]		[0.02, 0.62]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.06)	0.1 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.05)
95% CI	[0.14, 0.32]	[-0.04, 0.22]	[0.06, 0.24]	[-0.02, 0.23]	[0.13, 0.25]	[0.01, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.15		0.04		0.09	
95% CI	[-0.01, 0.30]		[-0.12, 0.20]		[-0.02, 0.20]	
p-value	0.0690		0.6020		0.1076	
Hedges' g	0.43		0.06		0.24	
95% CI	[0.01, 0.85]		[-0.35, 0.47]		[-0.05, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	3.6 (0.55)	3.7 (0.57)	3.7 (0.67)	3.6 (0.49)	3.7 (0.61)	3.7 (0.54)
Visit 13/ET						
n/N2	65/70	36/39	67/73	30/33	132/143	66/72
Mean (SD)	3.8 (0.73)	3.9 (0.71)	4.1 (0.88)	3.6 (0.68)	3.9 (0.82)	3.8 (0.71)
EAP						
n/N2	65/70	36/39	68/73	32/33	133/143	68/72
Mean (SD)	3.8 (0.60)	3.9 (0.60)	4.0 (0.85)	3.7 (0.49)	3.9 (0.75)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.4.14.1.s2
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.2 (0.11)	0.3 (0.08)	-0.0 (0.13)	0.2 (0.06)	0.1 (0.08)
95% CI	[-0.02, 0.29]	[-0.01, 0.41]	[0.18, 0.51]	[-0.29, 0.21]	[0.13, 0.35]	[-0.08, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.07		0.38		0.16	
95% CI	[-0.33, 0.19]		[0.08, 0.68]		[-0.04, 0.36]	
p-value	0.5879		0.0133		0.1073	
Hedges' g	-0.04		0.48		0.22	
95% CI	[-0.45, 0.36]		[0.05, 0.92]		[-0.08, 0.51]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.3 (0.07)	0.0 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[-0.02, 0.21]	[-0.00, 0.31]	[0.18, 0.46]	[-0.17, 0.24]	[0.12, 0.30]	[-0.04, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.06		0.29		0.12	
95% CI	[-0.25, 0.14]		[0.04, 0.54]		[-0.03, 0.28]	
p-value	0.5561		0.0230		0.1244	
Hedges' g	-0.04		0.42		0.21	
95% CI	[-0.44, 0.37]		[0.00, 0.85]		[-0.08, 0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_14_1_m_phos_sex.sas using SAS 9.4

Table 12.5.1.1.1.s2
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4258		0.1982		0.1099	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	40/71	19/33	38/71	26/39	78/142	45/72
Mean (SD)	46.4 (38.38)	39.2 (36.40)	32.1 (21.10)	35.9 (32.33)	39.5 (31.80)	37.3 (33.74)
Visit 13/ET						
n/N1	36/71	7/33	33/71	15/39	69/142	22/72
Mean (SD)	48.5 (43.08)	71.6 (105.49)	52.1 (51.91)	73.1 (52.84)	50.2 (47.19)	72.6 (71.00)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	11.2 (10.32)	28.4 (22.14)	19.1 (11.20)	33.6 (15.54)	15.1 (7.64)	30.9 (13.33)
95% CI	[-9.72, 32.15]	[-16.54, 73.27]	[-3.72, 41.92]	[1.97, 65.27]	[-0.13, 30.37]	[4.29, 57.48]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-17.15		-14.52		-15.77	
95% CI	[-66.77, 32.47]		[-53.64, 24.60]		[-46.48, 14.95]	
p-value	0.4878		0.4551		0.3094	
Hedges' g	-0.23		-0.23		-0.26	
95% CI	[-1.03, 0.57]		[-0.91, 0.45]		[-0.78, 0.26]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_5_1_1_1_m_fgf23_sex.sas using SAS 9.4

Table 12.5.1.1.1.s2
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	57/70	22/39	46/73	21/33	103/143	43/72
Mean (SD)	47.8 (58.43)	49.5 (34.04)	37.2 (27.36)	35.6 (27.31)	43.1 (47.25)	42.7 (31.37)
Visit 13/ET						
n/N2	41/70	19/39	42/73	13/33	83/143	32/72
Mean (SD)	53.9 (54.89)	47.7 (30.16)	67.0 (78.88)	49.4 (58.92)	60.5 (68.01)	48.4 (43.27)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	4.6 (8.21)	-4.8 (12.11)	40.0 (14.90)	11.6 (24.01)	21.7 (8.07)	2.3 (12.49)
95% CI	[-11.92, 21.04]	[-29.10, 19.54]	[9.92, 70.17]	[-36.88, 60.16]	[5.73, 37.77]	[-22.46, 27.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	9.34		28.41		19.40	
95% CI	[-20.05, 38.72]		[-28.81, 85.62]		[-10.14, 48.95]	
p-value	0.5263		0.3217		0.1954	
Hedges' g	0.17		0.39		0.29	
95% CI	[-0.40, 0.74]		[-0.27, 1.05]		[-0.14, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_5_1_1_1_m_fgf23_sex.sas using SAS 9.4

Table 12.4.12.1.2.s2
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6570		0.5868		0.4980	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	71/71	33/33	70/71	39/39	141/142	72/72
Mean (SD)	29.9 (10.81)	32.0 (11.56)	31.9 (10.52)	32.5 (10.19)	30.9 (10.68)	32.3 (10.76)
Visit 13/ET						
n/N1	66/71	32/33	65/71	32/39	131/142	64/72
Mean (SD)	30.1 (11.76)	32.2 (11.68)	31.3 (13.12)	32.1 (11.00)	30.7 (12.42)	32.1 (11.26)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.78)	-0.1 (1.12)	-0.7 (0.81)	-1.1 (1.16)	-0.2 (0.56)	-0.6 (0.81)
95% CI	[-1.18, 1.91]	[-2.29, 2.17]	[-2.32, 0.90]	[-3.38, 1.21]	[-1.27, 0.95]	[-2.20, 0.99]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.43		0.37		0.44	
95% CI	[-2.29, 3.15]		[-2.43, 3.18]		[-1.50, 2.39]	
p-value	0.7562		0.7935		0.6547	
Hedges' g	0.11		0.05		0.08	
95% CI	[-0.31, 0.53]		[-0.37, 0.47]		[-0.22, 0.38]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_2_m_egfr_sex.sas using SAS 9.4

Table 12.4.12.1.2.s2
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	70/70	39/39	73/73	33/33	143/143	72/72
Mean (SD)	30.7 (11.38)	32.6 (10.68)	30.0 (9.30)	30.9 (8.95)	30.4 (10.34)	31.8 (9.90)
Visit 13/ET						
n/N2	65/70	36/39	67/73	30/33	132/143	66/72
Mean (SD)	29.5 (12.01)	31.9 (11.19)	27.6 (9.45)	28.5 (9.92)	28.5 (10.78)	30.3 (10.69)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.3 (0.95)	-0.7 (1.28)	-2.0 (0.66)	-1.3 (0.99)	-1.6 (0.58)	-1.0 (0.82)
95% CI	[-3.16, 0.61]	[-3.21, 1.86]	[-3.32, -0.69]	[-3.31, 0.62]	[-2.77, -0.49]	[-2.65, 0.59]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.60		-0.66		-0.60	
95% CI	[-3.77, 2.57]		[-3.02, 1.70]		[-2.59, 1.38]	
p-value	0.7085		0.5808		0.5495	
Hedges' g	-0.02		-0.11		-0.06	
95% CI	[-0.43, 0.38]		[-0.54, 0.31]		[-0.36, 0.23]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_12_1_2_m_egfr_sex.sas using SAS 9.4

Table 12.4.15.1.1.s2
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2665		0.7542		0.5608	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
Baseline						
n/N1	57/71	24/33	47/71	26/39	104/142	50/72
Mean (SD)	0.5 (0.81)	0.6 (0.66)	0.6 (0.81)	0.7 (0.97)	0.6 (0.81)	0.7 (0.83)
Visit 13/ET						
n/N1	50/71	25/33	40/71	17/39	90/142	42/72
Mean (SD)	0.6 (1.08)	0.6 (0.78)	0.5 (0.72)	0.6 (0.72)	0.6 (0.93)	0.6 (0.75)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.10)	0.1 (0.14)	-0.0 (0.10)	-0.0 (0.16)	-0.0 (0.08)	0.0 (0.11)
95% CI	[-0.20, 0.19]	[-0.18, 0.38]	[-0.26, 0.16]	[-0.36, 0.28]	[-0.17, 0.13]	[-0.21, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.10		-0.01		-0.04	
95% CI	[-0.45, 0.24]		[-0.39, 0.37]		[-0.31, 0.23]	
p-value	0.5525		0.9638		0.7845	
Hedges' g	-0.15		0.05		-0.06	
95% CI	[-0.64, 0.33]		[-0.52, 0.63]		[-0.44, 0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_15_1_1_m_ua_sex.sas using SAS 9.4

Table 12.4.15.1.1.s2
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
Baseline						
n/N2	59/70	38/39	63/73	29/33	122/143	67/72
Mean (SD)	0.7 (0.72)	0.7 (1.02)	0.9 (1.16)	1.0 (1.39)	0.8 (0.97)	0.8 (1.20)
Visit 13/ET						
n/N2	55/70	35/39	57/73	26/33	112/143	61/72
Mean (SD)	0.8 (1.11)	0.7 (0.94)	1.2 (1.56)	1.1 (2.01)	1.0 (1.36)	0.9 (1.49)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	-0.0 (0.13)	0.2 (0.14)	0.3 (0.20)	0.2 (0.09)	0.1 (0.12)
95% CI	[-0.07, 0.35]	[-0.29, 0.23]	[-0.04, 0.52]	[-0.07, 0.74]	[0.02, 0.36]	[-0.09, 0.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		-0.10		0.04	
95% CI	[-0.16, 0.50]		[-0.59, 0.39]		[-0.25, 0.34]	
p-value	0.3118		0.6974		0.7702	
Hedges' g	0.21		-0.07		0.08	
95% CI	[-0.21, 0.63]		[-0.53, 0.40]		[-0.23, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_15_1_1_m_ua_sex.sas using SAS 9.4

Table 12.4.12.1.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5708		0.0714		0.4559	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	9.2 (0.28)	9.2 (0.27)	9.3 (0.33)	9.3 (0.26)	9.2 (0.31)	9.2 (0.26)
Visit 13/ET						
n/N1	67/73	33/36	72/77	26/29	139/150	59/65
Mean (SD)	9.4 (0.47)	9.3 (0.31)	9.5 (0.41)	9.4 (0.56)	9.5 (0.44)	9.4 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.04)	0.2 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.18, 0.36]	[-0.05, 0.20]	[0.17, 0.34]	[0.03, 0.32]	[0.20, 0.32]	[0.03, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.08		0.14	
95% CI	[0.03, 0.35]		[-0.09, 0.25]		[0.03, 0.25]	
p-value	0.0177		0.3382		0.0163	
Hedges' g	0.57		0.21		0.41	
95% CI	[0.15, 0.99]		[-0.23, 0.66]		[0.11, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_1_m_dca_wt.sas using SAS 9.4

Table 12.4.12.1.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	9.2 (0.29)	9.2 (0.29)	9.2 (0.37)	9.3 (0.30)	9.2 (0.33)	9.2 (0.30)
Visit 13/ET						
n/N2	64/68	35/36	60/67	36/43	124/135	71/79
Mean (SD)	9.6 (0.53)	9.4 (0.34)	9.5 (0.39)	9.3 (0.53)	9.5 (0.47)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.2 (0.07)	0.3 (0.04)	0.0 (0.06)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.22, 0.43]	[0.01, 0.29]	[0.23, 0.40]	[-0.07, 0.16]	[0.25, 0.39]	[0.01, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.27		0.22	
95% CI	[-0.00, 0.34]		[0.12, 0.41]		[0.11, 0.33]	
p-value	0.0545		0.0004		0.0002	
Hedges' g	0.40		0.78		0.57	
95% CI	[-0.01, 0.82]		[0.35, 1.20]		[0.28, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_1_m_dca_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4071		0.7514		0.4573	
Comparison Baseline vs. EAP	0.2317		0.4194		0.1839	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	3.8 (0.59)	3.9 (0.61)	3.8 (0.56)	3.7 (0.47)	3.8 (0.58)	3.8 (0.55)
Visit 13/ET						
n/N1	67/73	33/36	72/77	26/29	139/150	59/65
Mean (SD)	4.0 (0.79)	3.9 (0.55)	4.0 (0.67)	3.6 (0.62)	4.0 (0.73)	3.8 (0.60)
EAP						
n/N1	67/73	34/36	73/77	26/29	140/150	60/65
Mean (SD)	4.0 (0.70)	4.0 (0.50)	4.0 (0.66)	3.6 (0.51)	4.0 (0.68)	3.8 (0.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.07)	0.1 (0.10)	0.2 (0.07)	-0.1 (0.11)	0.2 (0.05)	-0.0 (0.08)
95% CI	[0.13, 0.41]	[-0.12, 0.29]	[0.05, 0.32]	[-0.35, 0.10]	[0.13, 0.32]	[-0.17, 0.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.31		0.24	
95% CI	[-0.07, 0.43]		[0.05, 0.58]		[0.06, 0.42]	
p-value	0.1499		0.0222		0.0094	
Hedges' g	0.35		0.38		0.35	
95% CI	[-0.07, 0.76]		[-0.07, 0.83]		[0.04, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.2 (0.06)	-0.1 (0.10)	0.2 (0.04)	0.0 (0.06)
95% CI	[0.15, 0.35]	[-0.02, 0.27]	[0.08, 0.31]	[-0.30, 0.09]	[0.14, 0.30]	[-0.10, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.30		0.20	
95% CI	[-0.06, 0.30]		[0.07, 0.53]		[0.06, 0.34]	
p-value	0.1816		0.0119		0.0061	
Hedges' g	0.33		0.45		0.37	
95% CI	[-0.08, 0.74]		[0.00, 0.90]		[0.06, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	67/67	43/43	135/135	79/79
Mean (SD)	3.7 (0.49)	3.8 (0.57)	3.7 (0.55)	3.7 (0.47)	3.7 (0.52)	3.7 (0.52)
Visit 13/ET						
n/N2	64/68	35/36	60/67	36/43	124/135	71/79
Mean (SD)	3.8 (0.59)	3.8 (0.76)	4.0 (0.82)	3.8 (0.76)	3.9 (0.72)	3.8 (0.75)
EAP						
n/N2	64/68	35/36	63/67	39/43	127/135	74/79
Mean (SD)	3.8 (0.51)	3.9 (0.65)	4.0 (0.72)	3.9 (0.53)	3.9 (0.63)	3.9 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.4.14.1.s3
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.1 (0.09)	0.3 (0.08)	0.1 (0.11)	0.2 (0.05)	0.1 (0.07)
95% CI	[-0.03, 0.25]	[-0.10, 0.27]	[0.15, 0.48]	[-0.07, 0.35]	[0.11, 0.32]	[-0.03, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.18		0.11	
95% CI	[-0.21, 0.26]		[-0.09, 0.44]		[-0.07, 0.28]	
p-value	0.8469		0.1835		0.2299	
Hedges' g	0.10		0.28		0.19	
95% CI	[-0.31, 0.51]		[-0.13, 0.69]		[-0.10, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.3 (0.06)	0.2 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[-0.03, 0.18]	[-0.02, 0.26]	[0.17, 0.40]	[0.03, 0.33]	[0.10, 0.26]	[0.05, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.10		0.03	
95% CI	[-0.22, 0.14]		[-0.09, 0.29]		[-0.09, 0.16]	
p-value	0.6470		0.2962		0.5985	
Hedges' g	-0.02		0.20		0.09	
95% CI	[-0.43, 0.39]		[-0.19, 0.60]		[-0.20, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_14_1_m_phos_wt.sas using SAS 9.4

Table 12.5.1.1.1.s3
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0913		0.7373		0.3450	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	46/73	20/36	42/77	22/29	88/150	42/65
Mean (SD)	36.0 (23.68)	39.7 (34.56)	37.4 (28.91)	35.2 (31.01)	36.7 (26.16)	37.3 (32.42)
Visit 13/ET						
n/N1	40/73	9/36	43/77	9/29	83/150	18/65
Mean (SD)	53.1 (58.81)	40.7 (27.24)	56.6 (54.41)	72.0 (63.58)	54.9 (56.25)	56.4 (50.11)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	22.1 (9.79)	-10.2 (22.35)	22.1 (11.89)	30.6 (22.99)	21.9 (7.63)	11.8 (15.98)
95% CI	[2.27, 41.89]	[-55.39, 35.08]	[-2.08, 46.23]	[-16.09, 77.37]	[6.73, 37.12]	[-20.06, 43.63]
Diff in LS-Mean [ER-Calcifediol - Placebo]	32.23		-8.56		10.14	
95% CI	[-17.88, 82.34]		[-61.66, 44.54]		[-25.53, 45.81]	
p-value	0.2007		0.7451		0.5729	
Hedges' g	0.65		0.09		0.33	
95% CI	[-0.16, 1.46]		[-0.68, 0.85]		[-0.23, 0.89]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_5_1_1_1_m_fgf23_wt.sas using SAS 9.4

Table 12.5.1.1.1.s3
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	51/68	21/36	42/67	25/43	93/135	46/79
Mean (SD)	57.4 (65.17)	49.6 (35.74)	32.4 (19.69)	36.2 (29.46)	46.1 (51.35)	42.3 (32.81)
Visit 13/ET						
n/N2	37/68	17/36	32/67	19/43	69/135	36/79
Mean (SD)	49.5 (37.60)	61.2 (69.66)	65.6 (84.18)	57.4 (53.24)	57.0 (63.60)	59.2 (60.66)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-4.4 (8.51)	7.0 (12.22)	40.7 (16.13)	20.1 (20.17)	17.2 (8.51)	12.7 (11.33)
95% CI	[-21.48, 12.74]	[-17.59, 31.50]	[8.03, 73.35]	[-20.74, 60.92]	[0.31, 34.15]	[-9.80, 35.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-11.32		20.60		4.52	
95% CI	[-41.25, 18.60]		[-31.69, 72.89]		[-23.64, 32.68]	
p-value	0.4506		0.4301		0.7506	
Hedges' g	-0.20		0.26		-0.01	
95% CI	[-0.77, 0.37]		[-0.36, 0.87]		[-0.43, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_5_1_1_1_m_fgf23_wt.sas using SAS 9.4

Table 12.4.12.1.2.s3
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3905		0.2142		0.1347	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	73/73	36/36	77/77	29/29	150/150	65/65
Mean (SD)	30.7 (11.02)	31.4 (11.76)	30.0 (9.61)	29.3 (8.97)	30.4 (10.29)	30.4 (10.58)
Visit 13/ET						
n/N1	67/73	33/36	72/77	26/29	139/150	59/65
Mean (SD)	29.1 (11.20)	31.8 (11.67)	28.1 (9.89)	29.0 (9.11)	28.6 (10.51)	30.6 (10.62)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.3 (0.74)	-0.4 (1.06)	-2.0 (0.59)	-0.8 (0.98)	-1.6 (0.47)	-0.6 (0.73)
95% CI	[-2.75, 0.20]	[-2.46, 1.75]	[-3.15, -0.82]	[-2.70, 1.18]	[-2.56, -0.70]	[-2.00, 0.87]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.92		-1.23		-1.06	
95% CI	[-3.50, 1.65]		[-3.49, 1.03]		[-2.77, 0.65]	
p-value	0.4794		0.2836		0.2217	
Hedges' g	-0.10		-0.25		-0.17	
95% CI	[-0.51, 0.31]		[-0.69, 0.20]		[-0.48, 0.13]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_2_m_egfr_wt.sas using SAS 9.4

Table 12.4.12.1.2.s3
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	68/68	36/36	66/67	43/43	134/135	79/79
Mean (SD)	29.9 (11.18)	33.3 (10.30)	32.1 (10.25)	33.4 (9.76)	31.0 (10.75)	33.4 (9.95)
Visit 13/ET						
n/N2	64/68	35/36	60/67	36/43	124/135	71/79
Mean (SD)	30.6 (12.52)	32.2 (11.18)	31.1 (13.11)	31.3 (11.54)	30.8 (12.76)	31.8 (11.29)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.99)	-0.4 (1.34)	-0.6 (0.89)	-1.6 (1.14)	-0.1 (0.67)	-1.0 (0.89)
95% CI	[-1.56, 2.36]	[-3.05, 2.27]	[-2.35, 1.16]	[-3.86, 0.68]	[-1.40, 1.25]	[-2.79, 0.71]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.80		1.00		0.97	
95% CI	[-2.52, 4.11]		[-1.88, 3.87]		[-1.23, 3.16]	
p-value	0.6345		0.4920		0.3872	
Hedges' g	0.15		0.14		0.15	
95% CI	[-0.25, 0.56]		[-0.27, 0.55]		[-0.14, 0.44]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_12_1_2_m_egfr_wt.sas using SAS 9.4

Table 12.4.15.1.1.s3
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9645		0.0707		0.1800	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
Baseline						
n/N1	62/73	32/36	59/77	24/29	121/150	56/65
Mean (SD)	0.6 (0.74)	0.6 (0.69)	0.7 (1.09)	0.7 (0.97)	0.7 (0.92)	0.7 (0.81)
Visit 13/ET						
n/N1	57/73	30/36	53/77	21/29	110/150	51/65
Mean (SD)	0.8 (1.30)	0.6 (0.88)	0.9 (1.42)	1.1 (2.02)	0.8 (1.35)	0.8 (1.46)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.11)	0.1 (0.15)	0.1 (0.14)	0.5 (0.22)	0.1 (0.09)	0.3 (0.13)
95% CI	[-0.09, 0.34]	[-0.20, 0.40]	[-0.19, 0.38]	[0.04, 0.92]	[-0.07, 0.28]	[0.03, 0.55]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		-0.39		-0.18	
95% CI	[-0.34, 0.39]		[-0.92, 0.14]		[-0.49, 0.13]	
p-value	0.8897		0.1470		0.2495	
Hedges' g	0.06		-0.34		-0.13	
95% CI	[-0.38, 0.50]		[-0.85, 0.16]		[-0.46, 0.20]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_15_1_1_m_ua_wt.sas using SAS 9.4

Table 12.4.15.1.1.s3
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
Baseline						
n/N2	54/68	30/36	51/67	31/43	105/135	61/79
Mean (SD)	0.6 (0.80)	0.7 (1.09)	0.8 (0.98)	1.0 (1.37)	0.7 (0.89)	0.9 (1.24)
Visit 13/ET						
n/N2	48/68	30/36	44/67	22/43	92/135	52/79
Mean (SD)	0.6 (0.80)	0.7 (0.87)	0.9 (1.20)	0.7 (1.17)	0.8 (1.02)	0.7 (1.00)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.08)	-0.0 (0.10)	0.2 (0.13)	-0.1 (0.19)	0.1 (0.08)	-0.1 (0.10)
95% CI	[-0.19, 0.14]	[-0.23, 0.18]	[-0.10, 0.43]	[-0.49, 0.27]	[-0.08, 0.22]	[-0.27, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		0.27		0.13	
95% CI	[-0.26, 0.26]		[-0.19, 0.74]		[-0.12, 0.39]	
p-value	0.9890		0.2455		0.2930	
Hedges' g	0.04		0.33		0.20	
95% CI	[-0.41, 0.50]		[-0.19, 0.85]		[-0.15, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_15_1_1_m_ua_wt.sas using SAS 9.4

Table 12.4.12.1.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5197		0.0048		0.0197	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	9.2 (0.28)	9.2 (0.30)	9.2 (0.33)	9.3 (0.27)	9.2 (0.31)	9.2 (0.29)
Visit 13/ET						
n/N1	78/85	45/48	90/98	40/46	168/183	85/94
Mean (SD)	9.5 (0.54)	9.3 (0.36)	9.6 (0.39)	9.3 (0.53)	9.5 (0.47)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.06)	0.3 (0.04)	0.0 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.24, 0.42]	[-0.01, 0.23]	[0.26, 0.41]	[-0.07, 0.15]	[0.27, 0.39]	[-0.01, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.22		0.29		0.26	
95% CI	[0.07, 0.38]		[0.16, 0.42]		[0.16, 0.36]	
p-value	0.0040		<0.0001		<0.0001	
Hedges' g	0.56		0.82		0.68	
95% CI	[0.18, 0.93]		[0.44, 1.21]		[0.41, 0.94]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_1_m_dca_race.sas using SAS 9.4

Table 12.4.12.1.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	9.2 (0.29)	9.3 (0.24)	9.3 (0.37)	9.3 (0.30)	9.3 (0.33)	9.3 (0.27)
Visit 13/ET						
n/N2	53/56	23/24	42/46	22/26	95/102	45/50
Mean (SD)	9.5 (0.44)	9.4 (0.23)	9.4 (0.41)	9.5 (0.55)	9.4 (0.42)	9.4 (0.42)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.2 (0.07)	0.2 (0.04)	0.2 (0.05)
95% CI	[0.14, 0.33]	[-0.01, 0.29]	[0.07, 0.28]	[0.06, 0.36]	[0.14, 0.28]	[0.06, 0.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.03		0.04	
95% CI	[-0.08, 0.28]		[-0.22, 0.15]		[-0.09, 0.17]	
p-value	0.2804		0.7165		0.5341	
Hedges' g	0.35		-0.10		0.15	
95% CI	[-0.13, 0.84]		[-0.61, 0.41]		[-0.20, 0.50]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_1_m_dca_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9246		0.0652		0.1571	
Comparison Baseline vs. EAP	0.9774		0.1061		0.2086	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	3.7 (0.57)	3.8 (0.61)	3.8 (0.54)	3.7 (0.41)	3.7 (0.55)	3.8 (0.52)
Visit 13/ET						
n/N1	78/85	45/48	90/98	40/46	168/183	85/94
Mean (SD)	4.0 (0.71)	3.9 (0.72)	4.0 (0.76)	3.6 (0.67)	4.0 (0.74)	3.8 (0.71)
EAP						
n/N1	78/85	45/48	93/98	40/46	171/183	85/94
Mean (SD)	3.9 (0.64)	4.0 (0.63)	4.0 (0.69)	3.7 (0.50)	4.0 (0.67)	3.8 (0.59)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.09)	0.3 (0.06)	-0.0 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.07, 0.34]	[-0.09, 0.27]	[0.16, 0.41]	[-0.24, 0.14]	[0.16, 0.34]	[-0.11, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.33		0.23	
95% CI	[-0.11, 0.34]		[0.10, 0.56]		[0.07, 0.39]	
p-value	0.3239		0.0051		0.0048	
Hedges' g	0.24		0.50		0.37	
95% CI	[-0.13, 0.61]		[0.13, 0.88]		[0.11, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.05)	0.0 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.07, 0.27]	[-0.01, 0.26]	[0.17, 0.36]	[-0.13, 0.17]	[0.15, 0.29]	[-0.03, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.24		0.15	
95% CI	[-0.12, 0.22]		[0.06, 0.42]		[0.03, 0.27]	
p-value	0.5866		0.0079		0.0156	
Hedges' g	0.16		0.47		0.32	
95% CI	[-0.21, 0.53]		[0.10, 0.85]		[0.06, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	46/46	26/26	102/102	50/50
Mean (SD)	3.7 (0.50)	3.8 (0.56)	3.8 (0.62)	3.7 (0.57)	3.7 (0.56)	3.7 (0.56)
Visit 13/ET						
n/N2	53/56	23/24	42/46	22/26	95/102	45/50
Mean (SD)	3.9 (0.70)	3.8 (0.54)	3.9 (0.70)	3.9 (0.76)	3.9 (0.70)	3.9 (0.65)
EAP						
n/N2	53/56	24/24	43/46	25/26	96/102	49/50
Mean (SD)	3.9 (0.60)	3.9 (0.48)	4.0 (0.67)	3.9 (0.56)	3.9 (0.63)	3.9 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.4.14.1.s4
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.11)	0.1 (0.09)	0.2 (0.13)	0.2 (0.06)	0.1 (0.08)
95% CI	[0.02, 0.31]	[-0.15, 0.29]	[-0.04, 0.33]	[-0.08, 0.44]	[0.04, 0.27]	[-0.04, 0.29]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.03		0.03	
95% CI	[-0.16, 0.37]		[-0.35, 0.29]		[-0.17, 0.23]	
p-value	0.4436		0.8337		0.7607	
Hedges' g	0.21		-0.09		0.05	
95% CI	[-0.27, 0.70]		[-0.60, 0.42]		[-0.30, 0.41]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.08)	0.2 (0.08)	0.1 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[0.06, 0.27]	[-0.03, 0.27]	[0.02, 0.33]	[-0.05, 0.35]	[0.07, 0.25]	[0.01, 0.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.02		0.02	
95% CI	[-0.14, 0.23]		[-0.23, 0.28]		[-0.13, 0.18]	
p-value	0.6553		0.8662		0.7670	
Hedges' g	0.15		-0.03		0.04	
95% CI	[-0.33, 0.63]		[-0.52, 0.45]		[-0.30, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_14_1_m_phos_race.sas using SAS 9.4

Table 12.5.1.1.1.s4
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5381		0.6501		0.6809	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	61/85	26/48	52/98	28/46	113/183	54/94
Mean (SD)	53.2 (60.64)	51.8 (36.74)	35.4 (26.62)	30.5 (21.85)	45.0 (48.71)	40.8 (31.56)
Visit 13/ET						
n/N1	46/85	20/48	53/98	12/46	99/183	32/94
Mean (SD)	57.7 (55.98)	57.2 (64.41)	60.5 (68.66)	57.6 (70.48)	59.2 (62.79)	57.3 (65.62)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.3 (9.14)	5.5 (14.13)	32.9 (12.74)	23.9 (23.43)	19.5 (7.62)	13.4 (13.01)
95% CI	[-11.05, 25.56]	[-22.80, 33.79]	[7.21, 58.52]	[-23.26, 71.12]	[4.35, 34.55]	[-12.37, 39.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.76		8.93		6.03	
95% CI	[-31.94, 35.46]		[-44.89, 62.74]		[-23.85, 35.92]	
p-value	0.9171		0.7399		0.6897	
Hedges' g	0.03		0.06		0.07	
95% CI	[-0.52, 0.57]		[-0.60, 0.72]		[-0.36, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_5_1_1_1_m_fgf23_race.sas using SAS 9.4

Table 12.5.1.1.1.s4
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	36/56	15/24	32/46	19/26	68/102	34/50
Mean (SD)	37.0 (25.11)	32.5 (29.23)	34.1 (21.64)	43.5 (38.18)	35.7 (23.41)	38.6 (34.47)
Visit 13/ET						
n/N2	31/56	6/24	22/46	16/26	53/102	22/50
Mean (SD)	41.9 (36.71)	44.1 (35.89)	60.5 (69.13)	65.5 (44.41)	49.6 (52.84)	59.6 (42.55)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.5 (7.69)	6.3 (16.33)	26.5 (16.37)	22.6 (18.83)	17.1 (8.43)	14.5 (13.49)
95% CI	[-8.17, 23.27]	[-27.07, 39.74]	[-7.06, 60.10]	[-16.02, 61.25]	[0.21, 33.97]	[-12.56, 41.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.21		3.91		2.64	
95% CI	[-36.07, 38.50]		[-48.40, 56.22]		[-29.72, 35.00]	
p-value	0.9474		0.8793		0.8709	
Hedges' g	0.35		0.29		0.21	
95% CI	[-0.52, 1.22]		[-0.42, 0.99]		[-0.33, 0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_5_1_1_1_m_fgf23_race.sas using SAS 9.4

Table 12.4.12.1.2.s4
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0176		0.0052		0.0002	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	85/85	48/48	98/98	46/46	183/183	94/94
Mean (SD)	28.8 (9.92)	31.3 (11.09)	29.9 (9.28)	30.4 (8.63)	29.4 (9.57)	30.9 (9.92)
Visit 13/ET						
n/N1	78/85	45/48	90/98	40/46	168/183	85/94
Mean (SD)	27.2 (9.87)	31.8 (12.10)	27.6 (9.56)	30.3 (10.72)	27.4 (9.68)	31.1 (11.43)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.5 (0.69)	0.7 (0.91)	-2.4 (0.52)	-0.3 (0.78)	-1.9 (0.43)	0.2 (0.60)
95% CI	[-2.87, -0.14]	[-1.12, 2.47]	[-3.42, -1.37]	[-1.82, 1.26]	[-2.77, -1.09]	[-1.02, 1.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-2.18		-2.11		-2.10	
95% CI	[-4.45, 0.08]		[-3.96, -0.26]		[-3.55, -0.65]	
p-value	0.0590		0.0255		0.0048	
Hedges' g	-0.29		-0.42		-0.36	
95% CI	[-0.65, 0.08]		[-0.80, -0.05]		[-0.62, -0.09]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_2_m_egfr_race.sas using SAS 9.4

Table 12.4.12.1.2.s4
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	56/56	24/24	45/46	26/26	101/102	50/50
Mean (SD)	32.6 (12.35)	34.3 (10.84)	33.2 (11.00)	34.2 (10.87)	32.9 (11.71)	34.3 (10.74)
Visit 13/ET						
n/N2	53/56	23/24	42/46	22/26	95/102	45/50
Mean (SD)	33.7 (13.44)	32.3 (9.92)	33.4 (14.19)	30.5 (10.53)	33.6 (13.71)	31.4 (10.15)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	1.0 (1.12)	-2.3 (1.70)	0.8 (1.16)	-2.8 (1.61)	0.9 (0.81)	-2.6 (1.18)
95% CI	[-1.18, 3.28]	[-5.72, 1.06]	[-1.52, 3.13]	[-6.06, 0.36]	[-0.67, 2.55]	[-4.95, -0.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.38		3.65		3.56	
95% CI	[-0.69, 7.44]		[-0.32, 7.62]		[0.73, 6.40]	
p-value	0.1019		0.0705		0.0141	
Hedges' g	0.46		0.49		0.47	
95% CI	[-0.03, 0.95]		[-0.03, 1.00]		[0.12, 0.83]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_12_1_2_m_egfr_race.sas using SAS 9.4

Table 12.4.15.1.1.s4
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6556		0.3566		0.5550	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
Baseline						
n/N1	68/85	43/48	75/98	34/46	143/183	77/94
Mean (SD)	0.6 (0.78)	0.6 (0.84)	0.8 (1.10)	0.8 (1.11)	0.7 (0.96)	0.7 (0.96)
Visit 13/ET						
n/N1	61/85	43/48	64/98	27/46	125/183	70/94
Mean (SD)	0.6 (1.05)	0.6 (0.84)	1.0 (1.45)	0.8 (1.14)	0.8 (1.28)	0.7 (0.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.10)	0.0 (0.11)	0.1 (0.10)	0.0 (0.16)	0.1 (0.07)	0.0 (0.10)
95% CI	[-0.19, 0.20]	[-0.22, 0.23]	[-0.07, 0.33]	[-0.30, 0.33]	[-0.07, 0.21]	[-0.18, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.00		0.11		0.06	
95% CI	[-0.29, 0.30]		[-0.26, 0.49]		[-0.18, 0.29]	
p-value	0.9920		0.5527		0.6456	
Hedges' g	-0.01		0.14		0.07	
95% CI	[-0.40, 0.38]		[-0.32, 0.59]		[-0.23, 0.36]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_15_1_1_m_ua_race.sas using SAS 9.4

Table 12.4.15.1.1.s4
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
Baseline						
n/N2	48/56	19/24	35/46	21/26	83/102	40/50
Mean (SD)	0.6 (0.75)	0.7 (1.03)	0.7 (0.88)	1.0 (1.37)	0.6 (0.80)	0.9 (1.22)
Visit 13/ET						
n/N2	44/56	17/24	33/46	16/26	77/102	33/50
Mean (SD)	0.8 (1.17)	0.7 (0.95)	0.8 (1.01)	1.0 (2.28)	0.8 (1.09)	0.9 (1.71)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.10)	0.1 (0.17)	0.1 (0.22)	0.4 (0.31)	0.2 (0.11)	0.2 (0.17)
95% CI	[-0.05, 0.37]	[-0.29, 0.41]	[-0.30, 0.59]	[-0.21, 1.04]	[-0.07, 0.38]	[-0.10, 0.58]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.27		-0.08	
95% CI	[-0.30, 0.51]		[-1.04, 0.50]		[-0.49, 0.32]	
p-value	0.6193		0.4827		0.6825	
Hedges' g	0.14		-0.21		-0.09	
95% CI	[-0.42, 0.71]		[-0.81, 0.38]		[-0.50, 0.33]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_15_1_1_m_ua_race.sas using SAS 9.4

Table 12.4.12.1.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4965		0.0424		0.4343	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	9.3 (0.29)	9.3 (0.28)	9.3 (0.35)	9.3 (0.25)	9.3 (0.32)	9.3 (0.26)
Visit 13/ET						
n/N1	64/71	35/36	72/80	28/35	136/151	63/71
Mean (SD)	9.5 (0.45)	9.3 (0.29)	9.5 (0.38)	9.5 (0.50)	9.5 (0.42)	9.4 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.04)	0.2 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.17, 0.35]	[-0.05, 0.19]	[0.19, 0.34]	[0.11, 0.34]	[0.21, 0.32]	[0.06, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.04		0.12	
95% CI	[0.04, 0.34]		[-0.10, 0.18]		[0.02, 0.22]	
p-value	0.0114		0.5542		0.0199	
Hedges' g	0.58		0.14		0.40	
95% CI	[0.17, 1.00]		[-0.30, 0.57]		[0.10, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_1_m_dca_ckd.sas using SAS 9.4

Table 12.4.12.1.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	9.1 (0.27)	9.2 (0.28)	9.2 (0.35)	9.2 (0.31)	9.2 (0.31)	9.2 (0.29)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	9.5 (0.55)	9.3 (0.36)	9.5 (0.42)	9.2 (0.55)	9.5 (0.49)	9.3 (0.47)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.2 (0.07)	0.3 (0.05)	0.0 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.22, 0.43]	[0.02, 0.31]	[0.20, 0.41]	[-0.13, 0.14]	[0.24, 0.39]	[-0.01, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.16		0.30		0.23	
95% CI	[-0.02, 0.34]		[0.14, 0.47]		[0.11, 0.35]	
p-value	0.0797		0.0005		0.0002	
Hedges' g	0.38		0.77		0.57	
95% CI	[-0.04, 0.80]		[0.34, 1.20]		[0.27, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_1_m_dca_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4333		0.8830		0.4747	
Comparison Baseline vs. EAP	0.8289		0.4238		0.6219	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	3.5 (0.51)	3.7 (0.55)	3.6 (0.52)	3.6 (0.43)	3.5 (0.52)	3.6 (0.49)
Visit 13/ET						
n/N1	64/71	35/36	72/80	28/35	136/151	63/71
Mean (SD)	3.6 (0.58)	3.8 (0.61)	3.7 (0.60)	3.6 (0.68)	3.7 (0.59)	3.7 (0.65)
EAP						
n/N1	64/71	35/36	74/80	31/35	138/151	66/71
Mean (SD)	3.6 (0.49)	3.8 (0.54)	3.7 (0.48)	3.6 (0.46)	3.7 (0.48)	3.7 (0.51)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.1 (0.06)	-0.0 (0.09)	0.1 (0.04)	0.1 (0.06)
95% CI	[0.01, 0.26]	[-0.01, 0.33]	[0.01, 0.24]	[-0.21, 0.16]	[0.05, 0.22]	[-0.06, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.15		0.07	
95% CI	[-0.24, 0.18]		[-0.07, 0.37]		[-0.08, 0.22]	
p-value	0.8074		0.1750		0.3703	
Hedges' g	0.10		0.30		0.18	
95% CI	[-0.31, 0.51]		[-0.14, 0.73]		[-0.12, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.1 (0.04)	0.0 (0.06)	0.1 (0.03)	0.1 (0.04)
95% CI	[0.05, 0.24]	[0.01, 0.27]	[0.03, 0.18]	[-0.07, 0.17]	[0.07, 0.19]	[0.00, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.06		0.04	
95% CI	[-0.16, 0.17]		[-0.08, 0.20]		[-0.07, 0.14]	
p-value	0.9234		0.3879		0.5042	
Hedges' g	0.19		0.16		0.17	
95% CI	[-0.22, 0.60]		[-0.25, 0.58]		[-0.12, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	64/64	37/37	134/134	73/73
Mean (SD)	3.9 (0.48)	4.0 (0.59)	4.0 (0.54)	3.8 (0.49)	4.0 (0.51)	3.9 (0.55)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	4.2 (0.72)	4.0 (0.71)	4.4 (0.74)	3.9 (0.71)	4.3 (0.73)	3.9 (0.71)
EAP						
n/N2	67/70	34/36	62/64	34/37	129/134	68/73
Mean (SD)	4.1 (0.65)	4.1 (0.57)	4.4 (0.72)	3.9 (0.57)	4.2 (0.69)	4.0 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.4.14.1.s5
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.0 (0.11)	0.4 (0.09)	0.0 (0.12)	0.3 (0.06)	0.0 (0.08)
95% CI	[0.08, 0.39]	[-0.20, 0.24]	[0.23, 0.58]	[-0.19, 0.28]	[0.20, 0.43]	[-0.12, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.22		0.37		0.28	
95% CI	[-0.05, 0.48]		[0.07, 0.66]		[0.09, 0.48]	
p-value	0.1123		0.0165		0.0049	
Hedges' g	0.33		0.34		0.33	
95% CI	[-0.08, 0.75]		[-0.08, 0.76]		[0.04, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.4 (0.07)	0.1 (0.10)	0.3 (0.05)	0.1 (0.06)
95% CI	[0.07, 0.29]	[-0.03, 0.28]	[0.25, 0.55]	[-0.14, 0.27]	[0.19, 0.38]	[-0.02, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.33		0.18	
95% CI	[-0.14, 0.25]		[0.08, 0.59]		[0.03, 0.34]	
p-value	0.5907		0.0101		0.0216	
Hedges' g	0.13		0.40		0.27	
95% CI	[-0.28, 0.54]		[-0.02, 0.82]		[-0.02, 0.57]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_14_1_m_phos_ckd.sas using SAS 9.4

Table 12.5.1.1.1.s5
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8531		0.1794		0.2804	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	40/71	15/36	41/80	21/35	81/151	36/71
Mean (SD)	41.6 (30.73)	47.2 (43.29)	35.7 (28.92)	29.1 (18.41)	38.6 (29.78)	36.6 (32.02)
Visit 13/ET						
n/N1	30/71	11/36	32/80	10/35	62/151	21/71
Mean (SD)	31.6 (22.58)	42.2 (32.99)	38.5 (27.83)	57.5 (46.40)	35.2 (25.45)	49.5 (39.67)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-8.9 (5.23)	-3.1 (8.39)	2.3 (8.37)	13.5 (13.25)	-3.8 (4.89)	6.3 (7.77)
95% CI	[-19.56, 1.82]	[-20.23, 14.08]	[-14.96, 19.51]	[-13.77, 40.80]	[-13.61, 5.98]	[-9.28, 21.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-5.80		-11.24		-10.10	
95% CI	[-26.08, 14.48]		[-43.54, 21.07]		[-28.50, 8.30]	
p-value	0.5633		0.4804		0.2761	
Hedges' g	0.01		-0.31		-0.18	
95% CI	[-0.74, 0.76]		[-1.11, 0.49]		[-0.73, 0.38]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_5_1_1_1_m_fgf23_ckd.sas using SAS 9.4

Table 12.5.1.1.1.s5
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	57/70	26/36	43/64	26/37	100/134	52/73
Mean (SD)	51.2 (61.18)	43.4 (30.25)	34.1 (20.22)	41.1 (36.11)	43.9 (48.61)	42.2 (33.00)
Visit 13/ET						
n/N2	47/70	15/36	43/64	18/37	90/134	33/73
Mean (SD)	63.9 (57.51)	62.9 (71.95)	76.8 (83.75)	64.7 (61.81)	70.1 (71.14)	63.9 (65.54)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	15.0 (9.10)	12.5 (15.95)	49.8 (14.18)	23.6 (20.83)	31.2 (8.14)	19.3 (12.94)
95% CI	[-3.23, 33.22]	[-19.47, 44.38]	[21.25, 78.29]	[-18.26, 65.53]	[15.02, 47.29]	[-6.35, 44.95]
Diff in LS-Mean [ER-Calcifediol - Placebo]	2.54		26.13		11.85	
95% CI	[-34.24, 39.32]		[-25.02, 77.29]		[-18.51, 42.21]	
p-value	0.8906		0.3093		0.4407	
Hedges' g	0.10		0.37		0.20	
95% CI	[-0.48, 0.67]		[-0.22, 0.96]		[-0.21, 0.61]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_5_1_1_1_m_fgf23_ckd.sas using SAS 9.4

Table 12.4.12.1.2.s5
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5312		0.8602		0.5998	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	71/71	36/36	80/80	35/35	151/151	71/71
Mean (SD)	38.4 (9.19)	40.3 (9.41)	37.4 (7.97)	39.0 (7.52)	37.9 (8.55)	39.6 (8.49)
Visit 13/ET						
n/N1	64/71	35/36	72/80	28/35	136/151	63/71
Mean (SD)	38.0 (9.55)	38.9 (9.54)	36.6 (10.34)	38.5 (8.25)	37.3 (9.97)	38.7 (8.92)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.90)	-0.8 (1.21)	-0.9 (0.84)	-0.4 (1.35)	-0.7 (0.62)	-0.6 (0.91)
95% CI	[-2.25, 1.31]	[-3.26, 1.56]	[-2.52, 0.80]	[-3.11, 2.24]	[-1.88, 0.55]	[-2.42, 1.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.38		-0.42		-0.04	
95% CI	[-2.62, 3.38]		[-3.57, 2.73]		[-2.21, 2.13]	
p-value	0.8040		0.7908		0.9700	
Hedges' g	0.12		-0.03		0.05	
95% CI	[-0.29, 0.53]		[-0.46, 0.41]		[-0.24, 0.35]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_2_m_egfr_ckd.sas using SAS 9.4

Table 12.4.12.1.2.s5
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	70/70	36/36	63/64	37/37	133/134	73/73
Mean (SD)	22.2 (5.32)	24.4 (5.38)	22.7 (4.73)	24.9 (5.50)	22.4 (5.04)	24.7 (5.41)
Visit 13/ET						
n/N2	67/70	33/36	60/64	34/37	127/134	67/73
Mean (SD)	22.0 (7.86)	24.7 (8.15)	20.9 (5.27)	23.7 (7.00)	21.4 (6.76)	24.2 (7.55)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.81)	0.3 (1.17)	-2.2 (0.57)	-1.4 (0.77)	-1.4 (0.51)	-0.5 (0.70)
95% CI	[-2.14, 1.10]	[-2.02, 2.62]	[-3.38, -1.10]	[-2.92, 0.13]	[-2.38, -0.38]	[-1.93, 0.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.82		-0.85		-0.83	
95% CI	[-3.67, 2.03]		[-2.78, 1.08]		[-2.55, 0.89]	
p-value	0.5698		0.3833		0.3421	
Hedges' g	-0.06		-0.08		-0.06	
95% CI	[-0.48, 0.35]		[-0.50, 0.34]		[-0.35, 0.24]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_12_1_2_m_egfr_ckd.sas using SAS 9.4

Table 12.4.15.1.1.s5
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6638		0.3660		0.7469	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
Baseline						
n/N1	54/71	28/36	55/80	21/35	109/151	49/71
Mean (SD)	0.4 (0.61)	0.4 (0.85)	0.6 (0.86)	0.8 (1.36)	0.5 (0.75)	0.6 (1.10)
Visit 13/ET						
n/N1	46/71	29/36	49/80	19/35	95/151	48/71
Mean (SD)	0.6 (1.08)	0.5 (0.96)	0.6 (0.95)	0.9 (1.25)	0.6 (1.01)	0.6 (1.09)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.10)	0.1 (0.13)	0.1 (0.11)	0.3 (0.18)	0.1 (0.08)	0.2 (0.11)
95% CI	[-0.04, 0.37]	[-0.20, 0.33]	[-0.13, 0.33]	[-0.06, 0.66]	[-0.02, 0.29]	[-0.04, 0.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.20		-0.05	
95% CI	[-0.24, 0.44]		[-0.63, 0.23]		[-0.31, 0.22]	
p-value	0.5540		0.3497		0.7310	
Hedges' g	0.15		-0.25		-0.03	
95% CI	[-0.32, 0.61]		[-0.79, 0.29]		[-0.38, 0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_15_1_1_m_ua_ckd.sas using SAS 9.4

Table 12.4.15.1.1.s5
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
Baseline						
n/N2	62/70	34/36	55/64	34/37	117/134	68/73
Mean (SD)	0.8 (0.84)	0.9 (0.90)	1.0 (1.16)	0.9 (1.12)	0.9 (1.00)	0.9 (1.01)
Visit 13/ET						
n/N2	59/70	31/36	48/64	24/37	107/134	55/73
Mean (SD)	0.8 (1.11)	0.8 (0.75)	1.2 (1.57)	0.9 (1.91)	1.0 (1.34)	0.9 (1.37)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.10)	-0.0 (0.13)	0.2 (0.16)	0.1 (0.23)	0.1 (0.09)	0.0 (0.13)
95% CI	[-0.20, 0.19]	[-0.28, 0.26]	[-0.16, 0.49]	[-0.39, 0.54]	[-0.10, 0.26]	[-0.23, 0.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.00		0.09		0.05	
95% CI	[-0.33, 0.33]		[-0.48, 0.65]		[-0.26, 0.37]	
p-value	0.9905		0.7610		0.7351	
Hedges' g	0.01		0.08		0.05	
95% CI	[-0.43, 0.44]		[-0.40, 0.57]		[-0.27, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_15_1_1_m_ua_ckd.sas using SAS 9.4

Table 12.4.12.1.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7403		0.7190		0.5798	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	9.3 (0.27)	9.2 (0.28)	9.3 (0.29)	9.3 (0.30)	9.3 (0.28)	9.3 (0.29)
Visit 13/ET						
n/N1	40/43	25/26	49/53	18/20	89/96	43/46
Mean (SD)	9.5 (0.48)	9.3 (0.34)	9.6 (0.33)	9.4 (0.63)	9.6 (0.41)	9.4 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.07)	0.3 (0.04)	0.2 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.10, 0.33]	[-0.06, 0.23]	[0.20, 0.38]	[0.03, 0.32]	[0.18, 0.33]	[0.03, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.12		0.13	
95% CI	[-0.05, 0.31]		[-0.06, 0.29]		[0.00, 0.25]	
p-value	0.1548		0.1789		0.0479	
Hedges' g	0.36		0.38		0.40	
95% CI	[-0.14, 0.86]		[-0.16, 0.92]		[0.04, 0.77]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_1_m_dca_ttlpth.sas using SAS 9.4

Table 12.4.12.1.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	9.2 (0.27)	9.2 (0.30)	9.3 (0.39)	9.3 (0.22)	9.2 (0.33)	9.3 (0.26)
Visit 13/ET						
n/N2	47/50	22/22	43/44	23/28	90/94	45/50
Mean (SD)	9.4 (0.41)	9.3 (0.31)	9.5 (0.39)	9.4 (0.40)	9.4 (0.41)	9.3 (0.36)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.1 (0.07)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.10, 0.29]	[-0.07, 0.22]	[0.12, 0.33]	[-0.07, 0.21]	[0.14, 0.28]	[-0.03, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.15		0.14	
95% CI	[-0.05, 0.30]		[-0.02, 0.33]		[0.01, 0.26]	
p-value	0.1568		0.0890		0.0293	
Hedges' g	0.42		0.41		0.42	
95% CI	[-0.08, 0.93]		[-0.10, 0.91]		[0.06, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_1_m_dca_ttlpth.sas using SAS 9.4

Table 12.4.12.1.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	9.1 (0.31)	9.2 (0.28)	9.1 (0.33)	9.2 (0.33)	9.1 (0.32)	9.2 (0.30)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	9.6 (0.59)	9.4 (0.31)	9.4 (0.45)	9.3 (0.61)	9.5 (0.53)	9.3 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.5 (0.07)	0.2 (0.10)	0.3 (0.06)	0.1 (0.09)	0.4 (0.05)	0.1 (0.07)
95% CI	[0.33, 0.61]		[0.21, 0.47]		[0.31, 0.50]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.28		0.28		0.28	
95% CI	[0.04, 0.52]		[0.07, 0.50]		[0.12, 0.44]	
p-value	0.0237		0.0114		0.0008	
Hedges' g	0.63		0.66		0.65	
95% CI	[0.11, 1.16]		[0.13, 1.20]		[0.28, 1.03]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_1_m_dca_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6889		0.5841		0.9897	
Comparison Baseline vs. EAP	0.2062		0.4883		0.9254	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	3.5 (0.50)	3.7 (0.53)	3.6 (0.52)	3.5 (0.49)	3.6 (0.51)	3.6 (0.51)
Visit 13/ET						
n/N1	40/43	25/26	49/53	18/20	89/96	43/46
Mean (SD)	3.7 (0.55)	3.8 (0.68)	3.9 (0.65)	3.5 (0.48)	3.8 (0.61)	3.7 (0.61)
EAP						
n/N1	40/43	25/26	52/53	18/20	92/96	43/46
Mean (SD)	3.7 (0.52)	3.8 (0.56)	3.9 (0.59)	3.6 (0.41)	3.8 (0.57)	3.7 (0.51)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.2 (0.11)	0.2 (0.07)	-0.0 (0.11)	0.2 (0.05)	0.1 (0.08)
95% CI	[-0.01, 0.33]	[-0.05, 0.38]	[0.11, 0.38]	[-0.24, 0.20]	[0.10, 0.32]	[-0.09, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.27		0.14	
95% CI	[-0.28, 0.27]		[0.00, 0.53]		[-0.04, 0.33]	
p-value	0.9696		0.0460		0.1338	
Hedges' g	0.09		0.47		0.26	
95% CI	[-0.40, 0.59]		[-0.07, 1.01]		[-0.11, 0.62]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.2 (0.05)	0.1 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.01, 0.26]	[0.04, 0.35]	[0.15, 0.35]	[-0.09, 0.25]	[0.12, 0.27]	[0.02, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.05		0.17		0.06	
95% CI	[-0.26, 0.15]		[-0.03, 0.36]		[-0.07, 0.20]	
p-value	0.5931		0.0946		0.3635	
Hedges' g	-0.03		0.40		0.17	
95% CI	[-0.53, 0.46]		[-0.14, 0.93]		[-0.19, 0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	3.7 (0.57)	3.9 (0.51)	3.7 (0.59)	3.7 (0.42)	3.7 (0.57)	3.8 (0.46)
Visit 13/ET						
n/N2	47/50	22/22	43/44	23/28	90/94	45/50
Mean (SD)	4.0 (0.70)	3.9 (0.67)	3.9 (0.71)	3.9 (0.90)	4.0 (0.70)	3.9 (0.79)
EAP						
n/N2	47/50	22/22	43/44	24/28	90/94	46/50
Mean (SD)	4.0 (0.55)	3.9 (0.56)	3.9 (0.58)	3.9 (0.63)	3.9 (0.56)	3.9 (0.59)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.0 (0.12)	0.2 (0.10)	0.2 (0.13)	0.2 (0.06)	0.1 (0.09)
95% CI	[0.05, 0.38]	[-0.22, 0.26]	[0.02, 0.40]	[-0.11, 0.41]	[0.09, 0.34]	[-0.09, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.06		0.13	
95% CI	[-0.10, 0.49]		[-0.26, 0.38]		[-0.08, 0.35]	
p-value	0.1871		0.7150		0.2253	
Hedges' g	0.40		0.10		0.24	
95% CI	[-0.10, 0.91]		[-0.41, 0.60]		[-0.11, 0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.1 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.13, 0.35]	[-0.11, 0.22]	[0.00, 0.27]	[-0.05, 0.31]	[0.10, 0.27]	[-0.03, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.01		0.10	
95% CI	[-0.01, 0.38]		[-0.21, 0.24]		[-0.05, 0.25]	
p-value	0.0642		0.9229		0.1876	
Hedges' g	0.55		0.02		0.27	
95% CI	[0.04, 1.06]		[-0.48, 0.51]		[-0.09, 0.62]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	47/47	24/24	95/95	48/48
Mean (SD)	3.9 (0.53)	4.0 (0.68)	4.0 (0.55)	3.8 (0.48)	3.9 (0.54)	3.9 (0.59)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	4.1 (0.80)	4.0 (0.65)	4.2 (0.83)	3.7 (0.62)	4.1 (0.82)	3.9 (0.64)
EAP						
n/N3	44/48	22/24	41/47	23/24	85/95	45/48
Mean (SD)	4.0 (0.74)	4.1 (0.62)	4.3 (0.80)	3.8 (0.48)	4.1 (0.78)	3.9 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.4.14.1.s6
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.1 (0.14)	0.3 (0.12)	-0.1 (0.16)	0.2 (0.07)	-0.0 (0.10)
95% CI	[-0.01, 0.36]		[0.06, 0.52]		[0.08, 0.37]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.39		0.23	
95% CI	[-0.22, 0.44]		[-0.01, 0.79]		[-0.02, 0.48]	
p-value	0.5206		0.0560		0.0747	
Hedges' g	0.19		0.35		0.28	
95% CI	[-0.32, 0.71]		[-0.17, 0.88]		[-0.09, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.11)	0.3 (0.10)	-0.0 (0.14)	0.2 (0.06)	0.1 (0.09)
95% CI	[-0.05, 0.26]		[0.14, 0.54]		[0.09, 0.34]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.37		0.16	
95% CI	[-0.28, 0.26]		[0.03, 0.72]		[-0.05, 0.37]	
p-value	0.9259		0.0327		0.1368	
Hedges' g	0.01		0.39		0.22	
95% CI	[-0.49, 0.52]		[-0.11, 0.90]		[-0.14, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_14_1_m_phos_ttlpth.sas using SAS 9.4

Table 12.5.1.1.1.s6
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7318		0.8697		0.9921	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	19/43	10/26	24/53	8/20	43/96	18/46
Mean (SD)	41.2 (34.97)	43.5 (38.63)	36.1 (31.75)	26.7 (16.37)	38.4 (32.90)	36.0 (31.22)
Visit 13/ET						
n/N1	15/43	6/26	25/53	5/20	40/96	11/46
Mean (SD)	35.8 (27.20)	46.6 (28.85)	40.9 (27.16)	31.6 (22.50)	39.0 (26.94)	39.8 (26.08)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-5.1 (6.49)	-2.9 (10.47)	10.1 (6.65)	-8.1 (10.78)	1.8 (5.11)	-3.8 (8.24)
95% CI	[-18.97, 8.69]	[-25.21, 19.43]	[-4.12, 24.24]	[-31.03, 14.93]	[-8.62, 12.22]	[-20.58, 13.05]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-2.25		18.11		5.57	
95% CI	[-28.52, 24.02]		[-9.01, 45.24]		[-14.22, 25.36]	
p-value	0.8574		0.1751		0.5702	
Hedges' g	-0.03		0.11		0.06	
95% CI	[-1.01, 0.95]		[-0.88, 1.09]		[-0.66, 0.77]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_5_1_1_1_m_fgf23_ttlpth.sas using SAS 9.4

Table 12.5.1.1.1.s6
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	38/50	13/22	26/44	18/28	64/94	31/50
Mean (SD)	36.4 (19.45)	31.7 (34.34)	37.1 (25.02)	25.8 (17.09)	36.6 (21.70)	28.3 (25.42)
Visit 13/ET						
n/N2	28/50	7/22	26/44	9/28	54/94	16/50
Mean (SD)	46.0 (46.97)	40.3 (42.87)	71.1 (79.63)	69.4 (50.06)	58.1 (65.38)	56.7 (47.89)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	13.4 (9.35)	-1.4 (18.94)	46.7 (19.58)	39.4 (35.16)	29.4 (10.11)	21.0 (19.02)
95% CI	[-5.76, 32.60]	[-40.30, 37.43]	[6.05, 87.28]	[-33.55, 112.29]	[9.09, 49.72]	[-17.17, 59.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	14.86		7.30		8.37	
95% CI	[-28.78, 58.49]		[-76.69, 91.28]		[-34.91, 51.65]	
p-value	0.4907		0.8587		0.6993	
Hedges' g	0.41		-0.01		0.11	
95% CI	[-0.47, 1.29]		[-0.90, 0.88]		[-0.52, 0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_5_1_1_1_m_fgf23_ttlpth.sas using SAS 9.4

Table 12.5.1.1.1.s6
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	40/48	18/24	34/47	21/24	74/95	39/48
Mean (SD)	60.4 (71.70)	54.9 (32.20)	32.4 (18.65)	47.7 (37.91)	47.5 (55.69)	51.0 (35.12)
Visit 13/ET						
n/N3	34/48	13/24	24/47	14/24	58/95	27/48
Mean (SD)	62.6 (57.05)	65.1 (75.08)	69.3 (82.05)	68.3 (66.16)	65.4 (67.91)	66.8 (69.23)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.9 (11.36)	9.9 (17.82)	33.8 (17.22)	20.5 (22.80)	18.7 (9.87)	17.7 (13.98)
95% CI	[-14.03, 31.80]		[-1.30, 68.88]		[-0.95, 38.39]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.98		13.24		0.98	
95% CI	[-43.62, 41.66]		[-46.77, 73.25]		[-33.22, 35.18]	
p-value	0.9633		0.6561		0.9547	
Hedges' g	0.01		0.28		0.11	
95% CI	[-0.62, 0.64]		[-0.39, 0.96]		[-0.35, 0.57]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_5_1_1_1_m_fgf23_ttlpth.sas using SAS 9.4

Table 12.4.12.1.2.s6
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7811		0.7099		0.9030	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	43/43	26/26	53/53	20/20	96/96	46/46
Mean (SD)	37.4 (12.72)	38.9 (11.92)	34.0 (10.63)	37.4 (8.67)	35.5 (11.67)	38.2 (10.55)
Visit 13/ET						
n/N1	40/43	25/26	49/53	18/20	89/96	43/46
Mean (SD)	36.2 (12.33)	37.7 (11.77)	33.3 (12.76)	35.5 (10.10)	34.6 (12.58)	36.8 (11.03)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.1 (1.15)	-0.7 (1.46)	-0.6 (0.99)	-1.4 (1.64)	-0.9 (0.77)	-0.9 (1.11)
95% CI	[-3.45, 1.16]	[-3.65, 2.19]	[-2.56, 1.40]	[-4.65, 1.92]	[-2.40, 0.63]	[-3.15, 1.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.42		0.79		0.06	
95% CI	[-4.14, 3.31]		[-3.06, 4.63]		[-2.62, 2.74]	
p-value	0.8244		0.6848		0.9659	
Hedges' g	-0.01		0.12		0.05	
95% CI	[-0.51, 0.48]		[-0.42, 0.65]		[-0.32, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_2_m_egfr_ttlpth.sas using SAS 9.4

Table 12.4.12.1.2.s6
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	50/50	22/22	44/44	28/28	94/94	50/50
Mean (SD)	29.1 (8.38)	30.8 (8.60)	31.2 (8.87)	32.4 (9.48)	30.1 (8.62)	31.7 (9.05)
Visit 13/ET						
n/N2	47/50	22/22	43/44	23/28	90/94	45/50
Mean (SD)	28.6 (9.91)	31.1 (10.53)	29.2 (10.60)	31.6 (11.30)	28.9 (10.19)	31.3 (10.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.2 (0.93)	0.4 (1.36)	-1.7 (0.90)	-1.3 (1.23)	-1.0 (0.65)	-0.5 (0.91)
95% CI	[-2.08, 1.62]	[-2.35, 3.07]	[-3.50, 0.10]	[-3.77, 1.16]	[-2.24, 0.31]	[-2.28, 1.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.59		-0.40		-0.49	
95% CI	[-3.88, 2.70]		[-3.46, 2.66]		[-2.71, 1.73]	
p-value	0.7197		0.7959		0.6623	
Hedges' g	-0.07		-0.07		-0.06	
95% CI	[-0.57, 0.43]		[-0.57, 0.43]		[-0.42, 0.29]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_2_m_egfr_ttlpth.sas using SAS 9.4

Table 12.4.12.1.2.s6
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	48/48	24/24	46/47	24/24	94/95	48/48
Mean (SD)	25.3 (8.60)	26.6 (8.26)	27.2 (8.94)	26.3 (7.64)	26.2 (8.78)	26.5 (7.87)
Visit 13/ET						
n/N3	44/48	21/24	40/47	21/24	84/95	42/48
Mean (SD)	25.3 (11.01)	26.2 (8.44)	25.0 (9.21)	24.6 (7.32)	25.1 (10.13)	25.4 (7.85)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (1.14)	-0.9 (1.66)	-1.9 (0.82)	-1.1 (1.13)	-0.9 (0.71)	-1.0 (1.00)
95% CI	[-2.25, 2.32]		[-3.56, -0.29]		[-2.34, 0.46]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.97		-0.84		0.08	
95% CI	[-3.07, 5.01]		[-3.63, 1.95]		[-2.34, 2.51]	
p-value	0.6327		0.5503		0.9456	
Hedges' g	0.17		-0.20		0.03	
95% CI	[-0.34, 0.69]		[-0.72, 0.33]		[-0.34, 0.40]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_12_1_2_m_egfr_ttlpth.sas using SAS 9.4

Table 12.4.15.1.1.s6
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3105		0.8220		0.3759	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
Baseline						
n/N1	32/43	21/26	35/53	12/20	67/96	33/46
Mean (SD)	0.7 (0.90)	0.5 (0.68)	0.5 (0.64)	0.7 (0.84)	0.6 (0.77)	0.5 (0.74)
Visit 13/ET						
n/N1	29/43	22/26	32/53	12/20	61/96	34/46
Mean (SD)	0.9 (1.31)	0.6 (0.98)	0.8 (1.10)	1.0 (1.52)	0.8 (1.20)	0.7 (1.19)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.12)	0.2 (0.14)	0.3 (0.17)	0.4 (0.27)	0.2 (0.10)	0.3 (0.14)
95% CI	[-0.13, 0.35]	[-0.12, 0.45]	[-0.07, 0.61]	[-0.15, 0.96]	[-0.01, 0.39]	[0.00, 0.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.05		-0.14		-0.10	
95% CI	[-0.43, 0.32]		[-0.79, 0.51]		[-0.44, 0.25]	
p-value	0.7845		0.6666		0.5851	
Hedges' g	0.00		-0.17		-0.04	
95% CI	[-0.55, 0.56]		[-0.85, 0.51]		[-0.47, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_15_1_1_m_ua_ttlpth.sas using SAS 9.4

Table 12.4.15.1.1.s6
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
Baseline						
n/N2	40/50	19/22	36/44	21/28	76/94	40/50
Mean (SD)	0.5 (0.64)	0.9 (1.32)	0.8 (1.08)	0.4 (0.72)	0.7 (0.88)	0.7 (1.07)
Visit 13/ET						
n/N2	41/50	20/22	35/44	16/28	76/94	36/50
Mean (SD)	0.6 (1.10)	0.7 (0.88)	0.9 (1.11)	0.5 (0.79)	0.8 (1.10)	0.6 (0.83)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.13)	-0.1 (0.18)	0.1 (0.12)	-0.1 (0.18)	0.1 (0.09)	-0.1 (0.13)
95% CI	[-0.17, 0.34]	[-0.48, 0.24]	[-0.13, 0.36]	[-0.42, 0.30]	[-0.07, 0.27]	[-0.34, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.17		0.19	
95% CI	[-0.24, 0.65]		[-0.26, 0.61]		[-0.12, 0.49]	
p-value	0.3619		0.4325		0.2230	
Hedges' g	0.36		0.11		0.25	
95% CI	[-0.18, 0.89]		[-0.48, 0.69]		[-0.14, 0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_15_1_1_m_ua_ttlpth.sas using SAS 9.4

Table 12.4.15.1.1.s6
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
Baseline						
n/N3	44/48	22/24	39/47	22/24	83/95	44/48
Mean (SD)	0.7 (0.78)	0.6 (0.54)	0.9 (1.25)	1.4 (1.52)	0.8 (1.03)	1.0 (1.20)
Visit 13/ET						
n/N3	35/48	18/24	30/47	15/24	65/95	33/48
Mean (SD)	0.7 (0.91)	0.6 (0.75)	1.0 (1.72)	1.2 (2.28)	0.8 (1.35)	0.9 (1.64)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.12)	0.1 (0.16)	0.1 (0.23)	0.1 (0.32)	0.0 (0.12)	0.1 (0.17)
95% CI	[-0.26, 0.21]		[-0.39, 0.53]		[-0.23, 0.25]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.12		-0.08		-0.13	
95% CI	[-0.52, 0.28]		[-0.87, 0.72]		[-0.55, 0.29]	
p-value	0.5517		0.8467		0.5323	
Hedges' g	-0.24		-0.07		-0.14	
95% CI	[-0.81, 0.32]		[-0.68, 0.54]		[-0.55, 0.28]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_15_1_1_m_ua_ttlpth.sas using SAS 9.4

Table 12.4.12.1.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3820		0.8430		0.4020	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	9.3 (0.31)	9.4 (0.36)	9.5 (0.39)	9.6 (0.17)	9.4 (0.38)	9.5 (0.28)
Visit 13/ET						
n/N1	17/18	5/5	29/32	4/5	46/50	9/10
Mean (SD)	9.7 (0.48)	9.5 (0.32)	9.8 (0.35)	9.8 (0.37)	9.8 (0.40)	9.6 (0.36)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.09)	0.1 (0.17)	0.4 (0.06)	0.2 (0.15)	0.4 (0.05)	0.1 (0.11)
95% CI	[0.20, 0.58]	[-0.27, 0.43]	[0.24, 0.47]	[-0.10, 0.51]	[0.26, 0.46]	[-0.08, 0.36]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.31		0.15		0.22	
95% CI	[-0.08, 0.70]		[-0.17, 0.48]		[-0.02, 0.47]	
p-value	0.1159		0.3511		0.0704	
Hedges' g	0.87		0.58		0.76	
95% CI	[-0.13, 1.86]		[-0.45, 1.61]		[0.04, 1.48]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_1_m_dca_dose.sas using SAS 9.4

Table 12.4.12.1.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	9.2 (0.27)	9.2 (0.27)	9.2 (0.29)	9.2 (0.26)	9.2 (0.28)	9.2 (0.26)
Visit 13/ET						
n/N2	106/108	62/63	95/98	56/61	201/206	118/124
Mean (SD)	9.4 (0.40)	9.3 (0.32)	9.5 (0.36)	9.3 (0.55)	9.4 (0.38)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.03)	0.1 (0.04)	0.3 (0.04)	0.1 (0.05)	0.3 (0.03)	0.1 (0.03)
95% CI	[0.18, 0.31]	[0.04, 0.21]	[0.19, 0.34]	[0.00, 0.20]	[0.21, 0.31]	[0.05, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.17		0.15	
95% CI	[0.02, 0.23]		[0.05, 0.29]		[0.07, 0.23]	
p-value	0.0237		0.0074		0.0004	
Hedges' g	0.40		0.47		0.44	
95% CI	[0.09, 0.72]		[0.14, 0.80]		[0.21, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_1_m_dca_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6373		0.5502		0.7414	
Comparison Baseline vs. EAP	0.4386		0.5553		0.6073	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	32/32	5/5	50/50	10/10
Mean (SD)	3.4 (0.59)	3.2 (0.50)	3.7 (0.37)	3.7 (0.51)	3.6 (0.49)	3.4 (0.54)
Visit 13/ET						
n/N1	17/18	5/5	29/32	4/5	46/50	9/10
Mean (SD)	3.8 (0.59)	3.7 (0.76)	3.9 (0.59)	3.5 (0.67)	3.9 (0.58)	3.6 (0.68)
EAP						
n/N1	17/18	5/5	31/32	5/5	48/50	10/10
Mean (SD)	3.7 (0.53)	3.6 (0.40)	3.9 (0.48)	3.7 (0.48)	3.8 (0.50)	3.6 (0.42)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.5 (0.14)	0.4 (0.25)	0.2 (0.09)	-0.2 (0.25)	0.3 (0.08)	0.1 (0.18)
95% CI	[0.18, 0.76]	[-0.13, 0.94]	[-0.03, 0.35]	[-0.69, 0.33]	[0.14, 0.46]	[-0.25, 0.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.07		0.34		0.20	
95% CI	[-0.54, 0.67]		[-0.20, 0.89]		[-0.19, 0.59]	
p-value	0.8234		0.2101		0.3168	
Hedges' g	-0.04		0.65		0.14	
95% CI	[-0.99, 0.92]		[-0.38, 1.68]		[-0.57, 0.84]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.3 (0.10)	0.4 (0.18)	0.2 (0.06)	-0.0 (0.14)	0.2 (0.05)	0.2 (0.12)
95% CI	[0.11, 0.53]	[-0.02, 0.74]	[0.05, 0.29]	[-0.32, 0.26]	[0.12, 0.34]	[-0.07, 0.39]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.20		0.07	
95% CI	[-0.48, 0.40]		[-0.11, 0.52]		[-0.19, 0.32]	
p-value	0.8504		0.2045		0.5868	
Hedges' g	-0.25		0.61		0.05	
95% CI	[-1.21, 0.71]		[-0.33, 1.54]		[-0.62, 0.72]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	3.8 (0.53)	3.9 (0.58)	3.8 (0.61)	3.7 (0.45)	3.8 (0.57)	3.8 (0.53)
Visit 13/ET						
n/N2	106/108	62/63	95/98	56/61	201/206	118/124
Mean (SD)	3.9 (0.73)	3.9 (0.66)	4.1 (0.78)	3.7 (0.71)	4.0 (0.76)	3.8 (0.69)
EAP						
n/N2	106/108	63/63	97/98	58/61	203/206	121/124
Mean (SD)	3.9 (0.64)	4.0 (0.59)	4.1 (0.73)	3.7 (0.53)	4.0 (0.68)	3.9 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.4.14.1.s7
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.07)	0.3 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.26]	[-0.09, 0.20]	[0.17, 0.43]	[-0.11, 0.22]	[0.14, 0.31]	[-0.05, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.24		0.17	
95% CI	[-0.08, 0.28]		[0.03, 0.46]		[0.03, 0.31]	
p-value	0.2918		0.0245		0.0156	
Hedges' g	0.21		0.32		0.26	
95% CI	[-0.11, 0.52]		[-0.01, 0.65]		[0.04, 0.49]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.04)	0.1 (0.05)	0.3 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.07, 0.23]	[-0.00, 0.21]	[0.18, 0.39]	[-0.05, 0.22]	[0.15, 0.28]	[0.01, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.20		0.12	
95% CI	[-0.09, 0.18]		[0.03, 0.37]		[0.01, 0.22]	
p-value	0.4984		0.0203		0.0272	
Hedges' g	0.15		0.31		0.23	
95% CI	[-0.16, 0.46]		[-0.02, 0.63]		[0.01, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_14_1_m_phos_dose.sas using SAS 9.4

Table 12.5.1.1.1.s7
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	NA		NA		0.9862	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	12/18	2/5	14/32	3/5	26/50	5/10
Mean (SD)	35.9 (22.88)	82.8 (85.91)	41.9 (30.88)	21.1 (6.30)	39.1 (27.12)	45.8 (54.81)
Visit 13/ET						
n/N1	9/18	1/5	12/32	1/5	21/50	2/10
Mean (SD)	26.2 (13.29)	18.2 (NA)	54.3 (74.61)	15.4 (NA)	42.2 (57.76)	16.8 (1.98)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-8.8 (4.72)	-17.7 (14.41)	15.9 (29.22)	-17.9 (90.74)	3.5 (14.42)	-17.8 (44.41)
95% CI	[-19.99, 2.34]	[-51.73, 16.40]	[-53.20, 84.99]	[-232.50, 196.61]	[-27.21, 34.28]	[-112.46, 76.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	8.84		33.84		21.34	
95% CI	[-27.14, 44.82]		[-193.26, 260.94]		[-78.74, 121.43]	
p-value	0.5795		0.7349		0.6559	
Hedges' g	NA		NA		0.11	
95% CI	NA		NA		[-1.29, 1.51]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_5_1_1_1_m_fgf23_dose.sas using SAS 9.4

Table 12.5.1.1.1.s7
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	75/108	38/63	61/98	42/61	136/206	80/124
Mean (SD)	48.2 (55.02)	42.8 (32.40)	34.2 (24.11)	32.9 (25.32)	41.9 (44.35)	37.6 (29.14)
Visit 13/ET						
n/N2	64/108	25/63	59/98	25/61	123/206	50/124
Mean (SD)	51.6 (49.37)	55.6 (59.41)	64.0 (69.23)	63.3 (58.33)	57.6 (59.80)	59.4 (58.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	6.6 (7.26)	7.0 (11.34)	38.4 (11.36)	28.6 (16.07)	21.8 (6.47)	17.3 (9.57)
95% CI	[-7.87, 21.06]	[-15.55, 29.62]	[15.67, 61.10]	[-3.52, 60.77]	[9.04, 34.63]	[-1.60, 36.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.44		9.76		4.52	
95% CI	[-27.28, 26.40]		[-29.63, 49.15]		[-18.33, 27.37]	
p-value	0.9742		0.6220		0.6963	
Hedges' g	0.08		0.16		0.10	
95% CI	[-0.40, 0.56]		[-0.36, 0.68]		[-0.26, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_5_1_1_1_m_fgf23_dose.sas using SAS 9.4

Table 12.4.12.1.2.s7
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0727		0.7806		0.4106	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	18/18	5/5	31/32	5/5	49/50	10/10
Mean (SD)	30.1 (9.96)	42.6 (13.48)	33.5 (10.51)	41.6 (7.54)	32.3 (10.34)	42.1 (10.31)
Visit 13/ET						
n/N1	17/18	5/5	29/32	4/5	46/50	9/10
Mean (SD)	30.1 (12.30)	37.8 (16.08)	33.1 (14.14)	42.0 (11.58)	32.0 (13.43)	39.7 (13.58)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	1.5 (1.46)	-6.5 (2.91)	-0.5 (1.56)	0.7 (4.29)	0.5 (1.16)	-2.7 (2.62)
95% CI	[-1.55, 4.56]	[-12.63, -0.43]	[-3.70, 2.68]	[-8.07, 9.45]	[-1.85, 2.79]	[-8.00, 2.53]
Diff in LS-Mean [ER-Calcifediol - Placebo]	8.04		-1.20		3.21	
95% CI	[0.89, 15.18]		[-10.57, 8.17]		[-2.67, 9.09]	
p-value	0.0296		0.7956		0.2784	
Hedges' g	0.95		-0.22		0.28	
95% CI	[-0.05, 1.95]		[-1.24, 0.81]		[-0.43, 0.99]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_2_m_egfr_dose.sas using SAS 9.4

Table 12.4.12.1.2.s7
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	108/108	63/63	98/98	61/61	206/206	124/124
Mean (SD)	30.0 (11.19)	31.5 (10.57)	30.1 (9.40)	31.5 (8.88)	30.1 (10.35)	31.5 (9.74)
Visit 13/ET						
n/N2	106/108	62/63	95/98	56/61	201/206	118/124
Mean (SD)	29.9 (11.74)	31.5 (10.99)	28.1 (10.16)	30.1 (9.92)	29.0 (11.04)	30.8 (10.47)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.70)	-0.1 (0.91)	-1.9 (0.57)	-1.4 (0.74)	-1.2 (0.46)	-0.8 (0.60)
95% CI	[-1.85, 0.90]	[-1.93, 1.67]	[-3.01, -0.77]	[-2.89, 0.03]	[-2.09, -0.30]	[-1.94, 0.41]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.34		-0.46		-0.43	
95% CI	[-2.61, 1.92]		[-2.30, 1.39]		[-1.91, 1.05]	
p-value	0.7649		0.6239		0.5701	
Hedges' g	-0.01		-0.06		-0.03	
95% CI	[-0.32, 0.30]		[-0.39, 0.27]		[-0.26, 0.19]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_12_1_2_m_egfr_dose.sas using SAS 9.4

Table 12.4.15.1.1.s7
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3622		0.1471		0.2412	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
Baseline						
n/N1	16/18	5/5	23/32	2/5	39/50	7/10
Mean (SD)	0.6 (0.87)	0.1 (0.07)	0.6 (0.83)	4.1 (2.27)	0.6 (0.83)	1.2 (2.17)
Visit 13/ET						
n/N1	13/18	5/5	18/32	2/5	31/50	7/10
Mean (SD)	0.5 (0.61)	0.1 (0.16)	0.9 (1.15)	2.7 (3.31)	0.7 (0.98)	0.9 (1.86)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.11)	-0.2 (0.18)	0.2 (0.25)	1.2 (0.77)	-0.0 (0.15)	0.6 (0.35)
95% CI	[-0.36, 0.11]	[-0.59, 0.18]	[-0.36, 0.69]	[-0.42, 2.81]	[-0.32, 0.29]	[-0.07, 1.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		-1.03		-0.65	
95% CI	[-0.38, 0.55]		[-2.74, 0.68]		[-1.42, 0.12]	
p-value	0.7113		0.2204		0.0959	
Hedges' g	-0.41		-0.96		-0.40	
95% CI	[-1.40, 0.58]		[-2.39, 0.47]		[-1.21, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_15_1_1_m_ua_dose.sas using SAS 9.4

Table 12.4.15.1.1.s7
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
Baseline						
n/N2	87/108	54/63	74/98	49/61	161/206	103/124
Mean (SD)	0.7 (0.78)	0.7 (0.94)	0.8 (1.01)	0.7 (0.97)	0.7 (0.89)	0.7 (0.95)
Visit 13/ET						
n/N2	87/108	54/63	72/98	40/61	159/206	94/124
Mean (SD)	0.7 (1.04)	0.7 (0.89)	0.8 (1.04)	0.6 (0.74)	0.8 (1.04)	0.7 (0.83)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.0 (0.09)	0.1 (0.08)	-0.1 (0.11)	0.1 (0.05)	-0.0 (0.07)
95% CI	[-0.07, 0.22]	[-0.15, 0.21]	[-0.08, 0.23]	[-0.27, 0.15]	[-0.03, 0.18]	[-0.15, 0.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.14		0.09	
95% CI	[-0.18, 0.28]		[-0.12, 0.40]		[-0.09, 0.26]	
p-value	0.6699		0.2970		0.3286	
Hedges' g	0.08		0.14		0.11	
95% CI	[-0.26, 0.42]		[-0.25, 0.53]		[-0.15, 0.36]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_15_1_1_m_ua_dose.sas using SAS 9.4

Table 12.4.12.1.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1264		0.0100		0.5799	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	9.2 (0.29)	9.2 (0.22)	9.3 (0.30)	9.1 (0.26)	9.2 (0.29)	9.2 (0.24)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	9.3 (0.45)	9.4 (0.35)	9.7 (0.41)	9.1 (0.44)	9.5 (0.47)	9.2 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.2 (0.11)	0.5 (0.07)	-0.0 (0.11)	0.3 (0.05)	0.1 (0.08)
95% CI	[-0.02, 0.33]	[-0.06, 0.41]	[0.31, 0.59]	[-0.25, 0.18]	[0.20, 0.41]	[-0.09, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.49		0.24	
95% CI	[-0.31, 0.27]		[0.23, 0.75]		[0.05, 0.43]	
p-value	0.8806		0.0006		0.0134	
Hedges' g	-0.05		1.56		0.63	
95% CI	[-0.77, 0.67]		[0.70, 2.41]		[0.09, 1.18]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_1_m_dca_vitd.sas using SAS 9.4

Table 12.4.12.1.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	9.2 (0.29)	9.2 (0.29)	9.2 (0.35)	9.3 (0.28)	9.2 (0.32)	9.3 (0.29)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	9.5 (0.51)	9.3 (0.32)	9.5 (0.39)	9.4 (0.55)	9.5 (0.45)	9.4 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.2 (0.03)	0.1 (0.05)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.24, 0.39]	[-0.00, 0.21]	[0.18, 0.32]	[0.03, 0.22]	[0.23, 0.33]	[0.04, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.22		0.12		0.17	
95% CI	[0.09, 0.34]		[0.00, 0.24]		[0.08, 0.26]	
p-value	0.0010		0.0421		0.0001	
Hedges' g	0.57		0.35		0.47	
95% CI	[0.25, 0.89]		[0.02, 0.68]		[0.24, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_1_m_dca_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2914		0.8361		0.5747	
Comparison Baseline vs. EAP	0.6734		0.7150		0.6574	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	3.7 (0.40)	4.0 (0.53)	3.8 (0.52)	3.9 (0.49)	3.7 (0.46)	4.0 (0.51)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	3.9 (0.50)	3.9 (0.82)	4.2 (0.99)	4.1 (0.65)	4.0 (0.79)	4.0 (0.73)
EAP						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	3.8 (0.43)	4.1 (0.51)	4.1 (0.80)	4.1 (0.51)	4.0 (0.67)	4.1 (0.50)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.13)	-0.0 (0.17)	0.4 (0.18)	0.2 (0.27)	0.3 (0.11)	0.1 (0.16)
95% CI	[-0.05, 0.48]	[-0.38, 0.32]	[-0.00, 0.72]	[-0.36, 0.75]	[0.07, 0.51]	[-0.23, 0.39]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.24		0.16		0.21	
95% CI	[-0.21, 0.69]		[-0.50, 0.82]		[-0.17, 0.60]	
p-value	0.2842		0.6154		0.2737	
Hedges' g	0.60		0.22		0.40	
95% CI	[-0.14, 1.33]		[-0.54, 0.98]		[-0.14, 0.93]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.09)	0.2 (0.12)	0.3 (0.13)	0.3 (0.19)	0.2 (0.08)	0.2 (0.11)
95% CI	[-0.13, 0.25]	[-0.04, 0.46]	[0.07, 0.59]	[-0.14, 0.66]	[0.05, 0.36]	[-0.01, 0.44]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.15		0.07		-0.01	
95% CI	[-0.47, 0.18]		[-0.40, 0.55]		[-0.29, 0.27]	
p-value	0.3592		0.7520		0.9339	
Hedges' g	0.01		0.14		0.11	
95% CI	[-0.71, 0.73]		[-0.62, 0.90]		[-0.42, 0.64]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	123/123	63/63	241/241	124/124
Mean (SD)	3.7 (0.57)	3.8 (0.59)	3.8 (0.57)	3.7 (0.46)	3.7 (0.57)	3.7 (0.53)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	3.9 (0.74)	3.9 (0.64)	4.0 (0.69)	3.7 (0.71)	4.0 (0.71)	3.8 (0.68)
EAP						
n/N2	112/118	58/61	115/123	56/63	227/241	114/124
Mean (SD)	3.9 (0.65)	3.9 (0.59)	4.0 (0.66)	3.7 (0.51)	3.9 (0.65)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.4.14.1.s8
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.08)	0.2 (0.05)	0.0 (0.08)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.08, 0.29]	[-0.05, 0.26]	[0.11, 0.33]	[-0.16, 0.16]	[0.13, 0.28]	[-0.06, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.22		0.15	
95% CI	[-0.10, 0.27]		[0.03, 0.41]		[0.02, 0.28]	
p-value	0.3798		0.0238		0.0239	
Hedges' g	0.16		0.30		0.23	
95% CI	[-0.15, 0.48]		[-0.02, 0.63]		[0.00, 0.46]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.06)	0.2 (0.04)	0.0 (0.06)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.10, 0.26]	[-0.00, 0.23]	[0.13, 0.31]	[-0.09, 0.16]	[0.14, 0.26]	[-0.01, 0.16]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.07		0.18		0.12	
95% CI	[-0.07, 0.21]		[0.03, 0.34]		[0.02, 0.23]	
p-value	0.3417		0.0182		0.0187	
Hedges' g	0.18		0.30		0.24	
95% CI	[-0.14, 0.50]		[-0.02, 0.62]		[0.02, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_14_1_m_phos_vitd.sas using SAS 9.4

Table 12.5.1.1.1.s8
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2819		0.7717		0.7396	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	15/23	6/11	13/21	4/9	28/44	10/20
Mean (SD)	52.5 (39.57)	44.7 (38.51)	31.7 (25.11)	39.7 (35.14)	42.8 (34.70)	42.7 (35.24)
Visit 13/ET						
n/N1	10/23	3/11	13/21	3/9	23/44	6/20
Mean (SD)	65.3 (33.14)	141.9 (141.27)	71.1 (109.65)	67.2 (44.27)	68.6 (83.76)	104.6 (102.17)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	14.4 (25.16)	101.8 (45.98)	59.2 (45.68)	25.5 (75.26)	37.4 (24.86)	60.9 (42.82)
95% CI	[-42.46, 71.36]	[-2.22, 205.79]	[-46.16, 164.53]	[-148.00, 199.08]	[-14.86, 89.59]	[-29.05, 150.88]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-87.33		33.65		-23.55	
95% CI	[-210.44, 35.77]		[-170.90, 238.19]		[-129.76, 82.65]	
p-value	0.1430		0.7143		0.6469	
Hedges' g	-0.52		0.32		-0.02	
95% CI	[-1.75, 0.70]		[-0.90, 1.54]		[-0.92, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_5_1_1_1_m_fgf23_vitd.sas using SAS 9.4

Table 12.5.1.1.1.s8
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	82/118	35/61	71/123	43/63	153/241	78/124
Mean (SD)	46.3 (52.85)	44.8 (35.08)	35.5 (24.77)	35.4 (29.79)	41.3 (42.43)	39.6 (32.40)
Visit 13/ET						
n/N2	67/118	23/61	62/123	25/63	129/241	48/124
Mean (SD)	49.3 (51.33)	42.7 (30.17)	58.2 (57.18)	61.5 (57.97)	53.6 (54.19)	52.5 (47.24)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	5.3 (6.20)	-5.1 (10.48)	26.2 (9.22)	22.3 (13.66)	15.4 (5.38)	8.5 (8.47)
95% CI	[-7.06, 17.62]	[-25.97, 15.75]	[7.78, 44.61]	[-4.97, 49.62]	[4.76, 26.01]	[-8.25, 25.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	10.39		3.87		6.90	
95% CI	[-13.85, 34.63]		[-29.12, 36.85]		[-12.93, 26.73]	
p-value	0.3959		0.8156		0.4927	
Hedges' g	0.20		0.12		0.14	
95% CI	[-0.29, 0.70]		[-0.39, 0.63]		[-0.22, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_5_1_1_1_m_fgf23_vitd.sas using SAS 9.4

Table 12.4.12.1.2.s8
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0922		0.9818		0.2645	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	23/23	11/11	21/21	9/9	44/44	20/20
Mean (SD)	28.8 (8.98)	32.8 (13.85)	32.3 (10.10)	26.3 (6.08)	30.5 (9.58)	29.9 (11.29)
Visit 13/ET						
n/N1	19/23	11/11	21/21	9/9	40/44	20/20
Mean (SD)	28.5 (10.71)	31.0 (12.85)	30.1 (13.82)	24.3 (7.75)	29.4 (12.31)	28.0 (11.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	2.1 (1.43)	-1.7 (1.90)	-2.6 (1.19)	-1.0 (1.86)	0.0 (0.93)	-1.9 (1.31)
95% CI	[-0.84, 5.03]	[-5.61, 2.20]	[-5.05, -0.15]	[-4.86, 2.76]	[-1.85, 1.86]	[-4.54, 0.73]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.79		-1.55		1.91	
95% CI	[-1.20, 8.79]		[-6.17, 3.06]		[-1.31, 5.13]	
p-value	0.1308		0.4958		0.2394	
Hedges' g	0.64		-0.03		0.29	
95% CI	[-0.10, 1.38]		[-0.79, 0.73]		[-0.24, 0.82]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_2_m_egfr_vitd.sas using SAS 9.4

Table 12.4.12.1.2.s8
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	118/118	61/61	122/123	63/63	240/241	124/124
Mean (SD)	30.6 (11.44)	32.2 (10.57)	30.7 (9.92)	32.5 (9.80)	30.7 (10.67)	32.4 (10.14)
Visit 13/ET						
n/N2	112/118	57/61	111/123	53/63	223/241	110/124
Mean (SD)	30.0 (12.05)	32.2 (11.14)	29.3 (11.09)	31.4 (10.70)	29.7 (11.56)	31.8 (10.89)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.8 (0.68)	-0.2 (0.95)	-1.3 (0.58)	-1.0 (0.84)	-1.1 (0.45)	-0.6 (0.64)
95% CI	[-2.18, 0.49]	[-2.07, 1.68]	[-2.40, -0.12]	[-2.64, 0.66]	[-1.93, -0.18]	[-1.83, 0.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.65		-0.27		-0.47	
95% CI	[-2.95, 1.66]		[-2.28, 1.74]		[-2.00, 1.06]	
p-value	0.5796		0.7909		0.5435	
Hedges' g	-0.05		-0.02		-0.04	
95% CI	[-0.37, 0.27]		[-0.35, 0.30]		[-0.27, 0.19]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_12_1_2_m_egfr_vitd.sas using SAS 9.4

Table 12.4.15.1.1.s8
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7682		0.0946		0.1457	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
Baseline						
n/N1	20/23	9/11	14/21	8/9	34/44	17/20
Mean (SD)	0.7 (0.86)	0.5 (0.87)	1.0 (1.26)	0.6 (0.75)	0.8 (1.03)	0.6 (0.79)
Visit 13/ET						
n/N1	13/23	8/11	13/21	6/9	26/44	14/20
Mean (SD)	0.8 (0.63)	0.2 (0.34)	1.2 (1.42)	0.5 (0.73)	1.0 (1.10)	0.3 (0.53)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.11)	-0.5 (0.14)	0.2 (0.20)	-0.3 (0.29)	0.0 (0.12)	-0.4 (0.17)
95% CI	[-0.33, 0.13]	[-0.77, -0.17]	[-0.20, 0.63]	[-0.96, 0.27]	[-0.20, 0.29]	[-0.72, -0.04]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.37		0.56		0.42	
95% CI	[-0.01, 0.75]		[-0.18, 1.31]		[0.00, 0.84]	
p-value	0.0558		0.1260		0.0480	
Hedges' g	0.17		0.75		0.47	
95% CI	[-0.67, 1.02]		[-0.20, 1.71]		[-0.17, 1.12]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_15_1_1_m_ua_vitd.sas using SAS 9.4

Table 12.4.15.1.1.s8
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
Baseline						
n/N2	96/118	53/61	96/123	47/63	192/241	100/124
Mean (SD)	0.6 (0.75)	0.7 (0.91)	0.7 (1.00)	0.9 (1.27)	0.7 (0.88)	0.8 (1.09)
Visit 13/ET						
n/N2	92/118	52/61	84/123	37/63	176/241	89/124
Mean (SD)	0.7 (1.15)	0.7 (0.91)	0.9 (1.30)	1.0 (1.73)	0.8 (1.22)	0.8 (1.31)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.10)	0.1 (0.11)	0.3 (0.17)	0.1 (0.07)	0.2 (0.09)
95% CI	[-0.05, 0.26]	[-0.13, 0.28]	[-0.10, 0.34]	[-0.08, 0.59]	[-0.02, 0.24]	[-0.02, 0.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		-0.13		-0.05	
95% CI	[-0.23, 0.28]		[-0.53, 0.27]		[-0.28, 0.18]	
p-value	0.8386		0.5220		0.6588	
Hedges' g	0.04		-0.13		-0.04	
95% CI	[-0.30, 0.38]		[-0.52, 0.26]		[-0.30, 0.21]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_15_1_1_m_ua_vitd.sas using SAS 9.4

Table 12.4.12.1.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5106		0.4089		0.9475	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	9.2 (0.29)	9.2 (0.29)	9.2 (0.32)	9.3 (0.23)	9.2 (0.31)	9.3 (0.26)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	9.5 (0.40)	9.3 (0.34)	9.4 (0.41)	9.4 (0.60)	9.5 (0.40)	9.3 (0.47)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.2 (0.05)	0.1 (0.07)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.19, 0.35]	[-0.02, 0.19]	[0.14, 0.33]	[-0.05, 0.24]	[0.19, 0.31]	[0.01, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.14		0.16	
95% CI	[0.05, 0.32]		[-0.03, 0.31]		[0.05, 0.27]	
p-value	0.0086		0.1002		0.0043	
Hedges' g	0.58		0.38		0.48	
95% CI	[0.17, 0.98]		[-0.06, 0.82]		[0.18, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_1_m_dca_bl25d.sas using SAS 9.4

Table 12.4.12.1.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	9.2 (0.28)	9.2 (0.28)	9.3 (0.37)	9.2 (0.32)	9.2 (0.33)	9.2 (0.30)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	9.5 (0.59)	9.4 (0.30)	9.6 (0.37)	9.3 (0.49)	9.6 (0.49)	9.3 (0.41)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.08)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.21, 0.42]	[-0.01, 0.31]	[0.25, 0.42]	[-0.02, 0.21]	[0.26, 0.39]	[0.03, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.24		0.20	
95% CI	[-0.03, 0.36]		[0.10, 0.39]		[0.08, 0.32]	
p-value	0.0926		0.0009		0.0010	
Hedges' g	0.38		0.64		0.50	
95% CI	[-0.05, 0.81]		[0.22, 1.06]		[0.20, 0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_1_m_dca_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9616		0.2478		0.3998	
Comparison Baseline vs. EAP	0.5208		0.7920		0.5386	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	3.7 (0.51)	3.8 (0.61)	3.8 (0.61)	3.7 (0.40)	3.8 (0.57)	3.7 (0.52)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	3.9 (0.67)	3.8 (0.65)	4.1 (0.84)	3.9 (0.77)	4.0 (0.76)	3.8 (0.70)
EAP						
n/N1	64/68	39/40	66/70	31/36	130/138	70/76
Mean (SD)	3.9 (0.52)	3.9 (0.59)	4.1 (0.76)	3.8 (0.56)	4.0 (0.65)	3.8 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.0 (0.09)	0.3 (0.08)	0.2 (0.12)	0.2 (0.05)	0.1 (0.08)
95% CI	[0.05, 0.34]	[-0.14, 0.24]	[0.10, 0.41]	[-0.05, 0.43]	[0.12, 0.33]	[-0.04, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.14		0.07		0.12	
95% CI	[-0.10, 0.38]		[-0.21, 0.36]		[-0.07, 0.30]	
p-value	0.2367		0.6209		0.2102	
Hedges' g	0.22		0.09		0.17	
95% CI	[-0.18, 0.62]		[-0.35, 0.53]		[-0.12, 0.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.06)	0.3 (0.06)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.05, 0.25]	[0.00, 0.25]	[0.13, 0.38]	[-0.07, 0.30]	[0.13, 0.29]	[0.01, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.15		0.09	
95% CI	[-0.14, 0.19]		[-0.08, 0.37]		[-0.04, 0.23]	
p-value	0.7594		0.1971		0.1774	
Hedges' g	0.06		0.23		0.16	
95% CI	[-0.33, 0.46]		[-0.19, 0.66]		[-0.13, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	74/74	36/36	147/147	68/68
Mean (SD)	3.7 (0.58)	3.9 (0.55)	3.7 (0.51)	3.7 (0.53)	3.7 (0.54)	3.8 (0.55)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	3.9 (0.74)	4.0 (0.67)	3.9 (0.63)	3.6 (0.64)	3.9 (0.68)	3.8 (0.68)
EAP						
n/N2	67/73	30/32	70/74	34/36	137/147	64/68
Mean (SD)	3.9 (0.71)	4.0 (0.57)	3.9 (0.61)	3.7 (0.50)	3.9 (0.66)	3.9 (0.55)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.4.14.1.s9
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.10)	0.2 (0.07)	-0.1 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.06, 0.33]	[-0.09, 0.32]	[0.08, 0.36]	[-0.28, 0.11]	[0.11, 0.30]	[-0.12, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.31		0.18	
95% CI	[-0.17, 0.33]		[0.07, 0.55]		[0.01, 0.35]	
p-value	0.5107		0.0125		0.0424	
Hedges' g	0.23		0.45		0.35	
95% CI	[-0.20, 0.66]		[0.04, 0.86]		[0.06, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.09)	0.2 (0.06)	0.0 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.07, 0.30]	[-0.07, 0.27]	[0.10, 0.32]	[-0.12, 0.19]	[0.12, 0.27]	[-0.04, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.18		0.12	
95% CI	[-0.12, 0.29]		[-0.02, 0.37]		[-0.02, 0.26]	
p-value	0.4150		0.0754		0.1010	
Hedges' g	0.25		0.31		0.29	
95% CI	[-0.17, 0.68]		[-0.10, 0.72]		[-0.01, 0.59]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_14_1_m_phos_bl25d.sas using SAS 9.4

Table 12.5.1.1.1.s9
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5361		0.5988		0.4660	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	45/68	23/40	39/70	24/36	84/138	47/76
Mean (SD)	41.8 (33.52)	46.0 (32.41)	31.5 (20.83)	35.8 (30.76)	37.0 (28.65)	40.8 (31.66)
Visit 13/ET						
n/N1	39/68	16/40	41/70	17/36	80/138	33/76
Mean (SD)	37.3 (28.30)	53.9 (71.30)	58.6 (75.13)	62.6 (66.28)	48.2 (57.94)	58.3 (67.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.8 (8.00)	12.8 (12.17)	32.2 (15.00)	27.0 (21.27)	16.7 (8.18)	19.1 (11.96)
95% CI	[-15.35, 16.86]	[-11.73, 37.27]	[1.81, 62.51]	[-16.03, 70.00]	[0.45, 32.96]	[-4.71, 42.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-12.01		5.18		-2.36	
95% CI	[-41.66, 17.64]		[-47.63, 57.98]		[-31.35, 26.63]	
p-value	0.4191		0.8439		0.8718	
Hedges' g	-0.08		0.07		-0.01	
95% CI	[-0.68, 0.52]		[-0.56, 0.70]		[-0.44, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_5_1_1_1_m_fgf23_bl25d.sas using SAS 9.4

Table 12.5.1.1.1.s9
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	52/73	18/32	45/74	23/36	97/147	41/68
Mean (SD)	51.9 (62.11)	43.2 (39.16)	37.8 (27.54)	35.7 (29.61)	45.4 (49.47)	39.0 (33.88)
Visit 13/ET						
n/N2	38/73	10/32	34/74	11/36	72/147	21/68
Mean (SD)	65.7 (61.53)	54.6 (32.99)	62.7 (60.15)	61.4 (37.90)	64.3 (60.47)	58.2 (34.93)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	12.9 (10.08)	-2.8 (19.89)	30.1 (11.41)	16.3 (18.45)	21.3 (7.68)	5.2 (13.64)
95% CI	[-7.44, 33.29]	[-42.92, 37.41]	[6.87, 53.31]	[-21.20, 53.87]	[6.00, 36.61]	[-21.93, 32.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	15.68		13.75		16.07	
95% CI	[-29.36, 60.71]		[-30.49, 57.98]		[-15.13, 47.26]	
p-value	0.4860		0.5315		0.3082	
Hedges' g	0.22		0.32		0.25	
95% CI	[-0.50, 0.94]		[-0.39, 1.04]		[-0.27, 0.76]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_5_1_1_1_m_fgf23_bl25d.sas using SAS 9.4

Table 12.4.12.1.2.s9
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0613		0.5428		0.0820	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	68/68	40/40	70/70	36/36	138/138	76/76
Mean (SD)	30.4 (11.58)	32.6 (12.13)	31.1 (10.54)	31.1 (9.08)	30.7 (11.03)	31.9 (10.75)
Visit 13/ET						
n/N1	64/68	38/40	65/70	28/36	129/138	66/76
Mean (SD)	30.0 (12.49)	30.8 (11.67)	29.1 (11.70)	27.7 (9.62)	29.5 (12.06)	29.5 (10.88)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.99)	-1.4 (1.29)	-1.5 (0.72)	-2.0 (1.09)	-0.6 (0.62)	-1.8 (0.87)
95% CI	[-1.81, 2.12]	[-3.92, 1.19]	[-2.90, -0.05]	[-4.17, 0.18]	[-1.83, 0.60]	[-3.49, -0.05]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.52		0.52		1.15	
95% CI	[-1.71, 4.75]		[-2.08, 3.12]		[-0.96, 3.26]	
p-value	0.3532		0.6934		0.2833	
Hedges' g	0.26		0.08		0.18	
95% CI	[-0.14, 0.66]		[-0.36, 0.52]		[-0.12, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_2_m_egfr_bl25d.sas using SAS 9.4

Table 12.4.12.1.2.s9
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	73/73	32/32	73/74	36/36	146/147	68/68
Mean (SD)	30.3 (10.64)	32.0 (9.64)	30.9 (9.37)	32.4 (10.19)	30.6 (10.00)	32.2 (9.87)
Visit 13/ET						
n/N2	67/73	30/32	67/74	34/36	134/147	64/68
Mean (SD)	29.6 (11.28)	33.5 (10.92)	29.8 (11.40)	32.6 (10.94)	29.7 (11.30)	33.0 (10.86)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.0 (0.72)	0.9 (1.07)	-1.3 (0.77)	-0.6 (1.08)	-1.2 (0.53)	0.2 (0.76)
95% CI	[-2.47, 0.38]	[-1.23, 3.03]	[-2.79, 0.26]	[-2.72, 1.58]	[-2.19, -0.12]	[-1.34, 1.67]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-1.95		-0.70		-1.32	
95% CI	[-4.51, 0.62]		[-3.34, 1.95]		[-3.15, 0.51]	
p-value	0.1349		0.6023		0.1551	
Hedges' g	-0.30		-0.11		-0.20	
95% CI	[-0.73, 0.12]		[-0.52, 0.30]		[-0.49, 0.10]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_12_1_2_m_egfr_bl25d.sas using SAS 9.4

Table 12.4.15.1.1.s9
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8698		0.3591		0.3822	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
Baseline						
n/N1	60/68	38/40	58/70	28/36	118/138	66/76
Mean (SD)	0.6 (0.74)	0.7 (0.92)	0.9 (1.19)	1.0 (1.36)	0.7 (0.99)	0.8 (1.13)
Visit 13/ET						
n/N1	58/68	34/40	50/70	20/36	108/138	54/76
Mean (SD)	0.6 (1.03)	0.6 (0.83)	1.1 (1.56)	0.8 (0.80)	0.8 (1.31)	0.7 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.09)	-0.0 (0.12)	0.2 (0.12)	-0.0 (0.20)	0.1 (0.07)	-0.0 (0.11)
95% CI	[-0.15, 0.21]	[-0.25, 0.22]	[-0.10, 0.40]	[-0.41, 0.40]	[-0.05, 0.24]	[-0.23, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.15		0.10	
95% CI	[-0.24, 0.34]		[-0.32, 0.63]		[-0.16, 0.37]	
p-value	0.7392		0.5202		0.4391	
Hedges' g	0.08		0.16		0.13	
95% CI	[-0.34, 0.50]		[-0.36, 0.69]		[-0.20, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_15_1_1_m_ua_bl25d.sas using SAS 9.4

Table 12.4.15.1.1.s9
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
Baseline						
n/N2	56/73	24/32	52/74	27/36	108/147	51/68
Mean (SD)	0.6 (0.80)	0.6 (0.87)	0.6 (0.83)	0.7 (1.03)	0.6 (0.81)	0.7 (0.95)
Visit 13/ET						
n/N2	47/73	26/32	47/74	23/36	94/147	49/68
Mean (SD)	0.8 (1.18)	0.6 (0.94)	0.7 (0.99)	1.0 (2.13)	0.8 (1.08)	0.8 (1.60)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.12)	0.1 (0.16)	0.1 (0.16)	0.3 (0.22)	0.1 (0.10)	0.2 (0.14)
95% CI	[-0.12, 0.35]	[-0.24, 0.40]	[-0.20, 0.44]	[-0.14, 0.75]	[-0.08, 0.31]	[-0.07, 0.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		-0.18		-0.08	
95% CI	[-0.37, 0.43]		[-0.73, 0.36]		[-0.42, 0.25]	
p-value	0.8723		0.5021		0.6160	
Hedges' g	0.03		-0.17		-0.08	
95% CI	[-0.45, 0.51]		[-0.67, 0.33]		[-0.43, 0.26]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; ITT: Intention-To-Treat; LS: Least Square; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_15_1_1_m_ua_bl25d.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalyse - Sicherheitsendpunkte Sicherheits-relevante sHPT-assoziierte Parameter (PP-Population)

Folgende Daten werden für die PP-Population

- Absolute Veränderung des Kalzium-Spiegels (mg/dl) im Serum
- Absolute Veränderung des Phosphat-Spiegels (mg/dl) im Serum
- Absolute Veränderung des FGF-23-Spiegels (pg/ml) im Serum
- Absolute Veränderung der eGFR (ml/min/1,73 m^2)
- Absolute Veränderung der Albuminausscheidung (g/g Kreatinin) im Urin

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.12.1.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5791		0.6380		0.9837	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	9.2 (0.29)	9.3 (0.27)	9.2 (0.32)	9.2 (0.30)	9.2 (0.30)	9.2 (0.28)
Visit 13/ET						
n/N1	51/51	28/28	40/40	25/26	91/91	53/54
Mean (SD)	9.5 (0.38)	9.3 (0.37)	9.5 (0.44)	9.3 (0.52)	9.5 (0.41)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.06)	0.2 (0.07)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.14, 0.34]	[-0.08, 0.19]	[0.21, 0.43]	[0.02, 0.30]	[0.21, 0.36]	[-0.00, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.16		0.19	
95% CI	[0.02, 0.36]		[-0.02, 0.35]		[0.07, 0.31]	
p-value	0.0257		0.0749		0.0029	
Hedges' g	0.57		0.46		0.52	
95% CI	[0.11, 1.04]		[-0.04, 0.96]		[0.17, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_m_dca_age_pp.sas using SAS 9.4

Table 12.4.12.1.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	9.2 (0.26)	9.2 (0.28)	9.2 (0.31)	9.3 (0.25)	9.2 (0.29)	9.3 (0.26)
Visit 13/ET						
n/N2	64/64	33/34	77/79	32/34	141/143	65/68
Mean (SD)	9.5 (0.42)	9.4 (0.29)	9.5 (0.34)	9.4 (0.58)	9.5 (0.38)	9.4 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.2 (0.05)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.21, 0.36]	[0.06, 0.28]	[0.21, 0.37]	[-0.05, 0.20]	[0.23, 0.34]	[0.04, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.21		0.16	
95% CI	[-0.02, 0.25]		[0.06, 0.37]		[0.06, 0.27]	
p-value	0.0862		0.0063		0.0015	
Hedges' g	0.39		0.62		0.51	
95% CI	[-0.03, 0.81]		[0.20, 1.03]		[0.21, 0.81]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_m_dca_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7973		0.4512		0.7277	
Comparison Baseline vs. EAP	0.3680		0.5516		0.3211	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	3.8 (0.52)	4.0 (0.57)	3.9 (0.63)	3.6 (0.49)	3.8 (0.57)	3.8 (0.56)
Visit 13/ET						
n/N1	51/51	28/28	40/40	25/26	91/91	53/54
Mean (SD)	3.9 (0.68)	4.0 (0.66)	4.2 (0.91)	3.7 (0.91)	4.0 (0.80)	3.8 (0.80)
EAP						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	4.0 (0.56)	4.0 (0.50)	4.2 (0.79)	3.7 (0.66)	4.0 (0.68)	3.9 (0.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.0 (0.11)	0.3 (0.12)	0.0 (0.15)	0.2 (0.07)	0.0 (0.09)
95% CI	[-0.10, 0.23]	[-0.17, 0.26]	[0.09, 0.56]	[-0.30, 0.30]	[0.07, 0.34]	[-0.17, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.32		0.20	
95% CI	[-0.26, 0.29]		[-0.06, 0.71]		[-0.02, 0.43]	
p-value	0.8933		0.0996		0.0809	
Hedges' g	0.13		0.41		0.26	
95% CI	[-0.33, 0.59]		[-0.09, 0.91]		[-0.07, 0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.1 (0.08)	0.3 (0.09)	0.0 (0.11)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.01, 0.24]	[-0.07, 0.24]	[0.09, 0.45]	[-0.20, 0.25]	[0.10, 0.30]	[-0.09, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.24		0.16	
95% CI	[-0.15, 0.23]		[-0.05, 0.53]		[-0.00, 0.33]	
p-value	0.6807		0.0967		0.0544	
Hedges' g	0.22		0.36		0.29	
95% CI	[-0.24, 0.68]		[-0.13, 0.85]		[-0.05, 0.62]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	3.7 (0.55)	3.7 (0.57)	3.7 (0.54)	3.6 (0.40)	3.7 (0.54)	3.6 (0.49)
Visit 13/ET						
n/N2	64/64	33/34	77/79	32/34	141/143	65/68
Mean (SD)	3.9 (0.73)	3.7 (0.63)	3.9 (0.59)	3.8 (0.55)	3.9 (0.66)	3.8 (0.58)
EAP						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	3.8 (0.66)	3.8 (0.62)	4.0 (0.59)	3.8 (0.42)	3.9 (0.63)	3.8 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.4.14.1.s1.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.10)	0.2 (0.06)	0.1 (0.09)	0.2 (0.05)	0.1 (0.07)
95% CI	[0.11, 0.39]	[-0.08, 0.31]	[0.10, 0.33]	[-0.08, 0.27]	[0.14, 0.32]	[-0.03, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.12		0.12	
95% CI	[-0.11, 0.37]		[-0.09, 0.33]		[-0.03, 0.28]	
p-value	0.2860		0.2546		0.1254	
Hedges' g	0.21		0.16		0.18	
95% CI	[-0.21, 0.63]		[-0.25, 0.57]		[-0.11, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.2 (0.07)	0.2 (0.05)	0.1 (0.07)	0.2 (0.03)	0.2 (0.05)
95% CI	[0.06, 0.26]	[0.04, 0.32]	[0.15, 0.33]	[-0.00, 0.28]	[0.13, 0.27]	[0.07, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.10		0.03	
95% CI	[-0.20, 0.15]		[-0.07, 0.27]		[-0.09, 0.15]	
p-value	0.7592		0.2405		0.5992	
Hedges' g	-0.06		0.17		0.06	
95% CI	[-0.48, 0.35]		[-0.23, 0.57]		[-0.22, 0.35]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_14_1_m_phos_age_pp.sas using SAS 9.4

Table 12.5.1.1.1.s1.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2080		0.7707		0.8212	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	34/51	15/28	24/40	17/26	58/91	32/54
Mean (SD)	43.3 (35.35)	35.9 (19.94)	39.3 (31.56)	31.6 (20.63)	41.6 (33.61)	33.6 (20.10)
Visit 13/ET						
n/N1	30/51	12/28	26/40	12/26	56/91	24/54
Mean (SD)	43.1 (31.25)	34.0 (28.77)	76.2 (93.03)	65.2 (63.69)	58.5 (68.75)	49.6 (50.88)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	5.6 (5.31)	-12.5 (8.42)	53.2 (23.91)	32.3 (36.31)	28.0 (10.55)	12.4 (16.22)
95% CI	[-5.25, 16.40]	[-29.61, 4.68]	[3.74, 102.66]	[-42.86, 107.37]	[6.92, 49.17]	[-20.08, 44.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	18.04		20.94		15.64	
95% CI	[-2.26, 38.35]		[-70.21, 112.10]		[-23.17, 54.46]	
p-value	0.0797		0.6390		0.4229	
Hedges' g	0.70		0.03		0.16	
95% CI	[-0.04, 1.43]		[-0.77, 0.84]		[-0.39, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_5_1_1_1_m_fgf23_age_pp.sas using SAS 9.4

Table 12.5.1.1.1.s1.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	46/64	20/34	45/79	22/34	91/143	42/68
Mean (SD)	50.3 (64.09)	48.2 (43.41)	31.9 (21.12)	36.1 (29.51)	41.2 (48.55)	41.8 (36.83)
Visit 13/ET						
n/N2	39/64	10/34	41/79	13/34	80/143	23/68
Mean (SD)	52.5 (56.68)	52.2 (33.02)	52.1 (51.21)	61.5 (55.49)	52.3 (53.60)	57.5 (46.34)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	3.4 (9.12)	1.0 (17.31)	25.5 (10.24)	20.2 (15.72)	13.4 (6.87)	12.3 (11.70)
95% CI	[-15.00, 21.80]	[-33.87, 35.96]	[4.79, 46.20]	[-11.60, 51.93]	[-0.28, 27.05]	[-10.95, 35.57]
Diff in LS-Mean [ER-Calcifediol - Placebo]	2.35		5.33		1.07	
95% CI	[-37.12, 41.82]		[-32.99, 43.65]		[-25.93, 28.08]	
p-value	0.9050		0.7800		0.9372	
Hedges' g	0.05		0.19		0.07	
95% CI	[-0.64, 0.74]		[-0.45, 0.83]		[-0.40, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_5_1_1_1_m_fgf23_age_pp.sas using SAS 9.4

Table 12.4.12.1.2.s1.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3102		0.9354		0.4909	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	51/51	28/28	40/40	26/26	91/91	54/54
Mean (SD)	29.9 (12.65)	31.9 (10.54)	29.6 (10.23)	32.2 (9.11)	29.8 (11.59)	32.1 (9.78)
Visit 13/ET						
n/N1	51/51	28/28	40/40	25/26	91/91	53/54
Mean (SD)	29.1 (12.38)	32.0 (11.88)	29.1 (13.80)	31.1 (10.71)	29.1 (12.95)	31.6 (11.24)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.0 (0.98)	0.3 (1.32)	-0.4 (1.14)	-0.7 (1.44)	-0.7 (0.76)	-0.2 (0.99)
95% CI	[-2.90, 0.99]	[-2.35, 2.90]	[-2.71, 1.84]	[-3.58, 2.18]	[-2.22, 0.77]	[-2.12, 1.78]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-1.23		0.27		-0.56	
95% CI	[-4.50, 2.04]		[-3.42, 3.95]		[-3.02, 1.90]	
p-value	0.4555		0.8855		0.6537	
Hedges' g	-0.13		0.01		-0.06	
95% CI	[-0.58, 0.33]		[-0.48, 0.51]		[-0.40, 0.27]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_2_m_egfr_age_pp.sas using SAS 9.4

Table 12.4.12.1.2.s1.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population

Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	64/64	34/34	79/79	34/34	143/143	68/68
Mean (SD)	30.6 (9.56)	34.5 (11.48)	31.4 (9.05)	32.7 (9.49)	31.0 (9.26)	33.6 (10.49)
Visit 13/ET						
n/N2	64/64	33/34	77/79	32/34	141/143	65/68
Mean (SD)	30.7 (11.36)	33.6 (11.16)	29.2 (9.75)	30.7 (10.75)	29.9 (10.50)	32.2 (10.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.94)	-0.9 (1.32)	-1.8 (0.61)	-1.7 (0.94)	-1.0 (0.54)	-1.3 (0.80)
95% CI	[-1.98, 1.75]	[-3.51, 1.72]	[-3.04, -0.64]	[-3.56, 0.17]	[-2.03, 0.12]	[-2.92, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.78		-0.15		0.38	
95% CI	[-2.46, 4.02]		[-2.37, 2.07]		[-1.54, 2.30]	
p-value	0.6347		0.8949		0.6941	
Hedges' g	0.19		-0.01		0.09	
95% CI	[-0.22, 0.61]		[-0.42, 0.40]		[-0.20, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_12_1_2_m_egfr_age_pp.sas using SAS 9.4

Table 12.4.15.1.1.s1.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0149		0.9211		0.0812	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
Baseline						
n/N1	42/51	22/28	35/40	22/26	77/91	44/54
Mean (SD)	0.6 (0.68)	0.7 (0.70)	0.8 (1.11)	1.0 (1.47)	0.7 (0.90)	0.9 (1.14)
Visit 13/ET						
n/N1	43/51	24/28	34/40	20/26	77/91	44/54
Mean (SD)	0.5 (0.55)	0.9 (1.01)	0.9 (1.10)	0.6 (0.70)	0.7 (0.85)	0.7 (0.88)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.09)	0.2 (0.12)	0.1 (0.11)	-0.1 (0.15)	0.0 (0.07)	0.0 (0.09)
95% CI	[-0.25, 0.09]	[-0.05, 0.42]	[-0.13, 0.33]	[-0.39, 0.20]	[-0.13, 0.15]	[-0.13, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.26		0.19		-0.04	
95% CI	[-0.55, 0.03]		[-0.18, 0.56]		[-0.27, 0.19]	
p-value	0.0758		0.3131		0.7406	
Hedges' g	-0.40		0.17		-0.12	
95% CI	[-0.90, 0.10]		[-0.38, 0.72]		[-0.49, 0.25]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_15_1_1_m_ua_age_pp.sas using SAS 9.4

Table 12.4.15.1.1.s1.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Age≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
Baseline						
n/N2	51/64	31/34	54/79	24/34	105/143	55/68
Mean (SD)	0.7 (0.87)	0.6 (1.11)	0.6 (0.85)	0.6 (0.95)	0.6 (0.85)	0.6 (1.03)
Visit 13/ET						
n/N2	50/64	30/34	52/79	19/34	102/143	49/68
Mean (SD)	0.8 (1.29)	0.5 (0.75)	0.8 (1.03)	0.6 (0.80)	0.8 (1.16)	0.5 (0.77)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.10)	-0.1 (0.13)	0.1 (0.11)	-0.0 (0.18)	0.2 (0.07)	-0.1 (0.11)
95% CI	[-0.00, 0.39]	[-0.37, 0.14]	[-0.09, 0.33]	[-0.39, 0.33]	[0.01, 0.30]	[-0.29, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.31		0.15		0.24	
95% CI	[-0.01, 0.64]		[-0.27, 0.57]		[-0.02, 0.50]	
p-value	0.0571		0.4733		0.0734	
Hedges' g	0.44		0.21		0.33	
95% CI	[-0.02, 0.89]		[-0.33, 0.74]		[-0.01, 0.68]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_15_1_1_m_ua_age_pp.sas using SAS 9.4

Table 12.4.12.1.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9594		0.2631		0.4478	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	9.2 (0.27)	9.3 (0.22)	9.3 (0.31)	9.3 (0.26)	9.3 (0.30)	9.3 (0.24)
Visit 13/ET						
n/N1	59/59	28/29	58/59	30/31	117/118	58/60
Mean (SD)	9.5 (0.43)	9.4 (0.35)	9.7 (0.37)	9.5 (0.61)	9.6 (0.41)	9.4 (0.50)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.19, 0.37]	[-0.02, 0.25]	[0.21, 0.41]	[0.02, 0.30]	[0.23, 0.36]	[0.04, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.16		0.15		0.16	
95% CI	[0.00, 0.32]		[-0.02, 0.32]		[0.04, 0.27]	
p-value	0.0441		0.0898		0.0081	
Hedges' g	0.49		0.38		0.43	
95% CI	[0.03, 0.94]		[-0.06, 0.82]		[0.11, 0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_1_m_dca_sex_pp.sas using SAS 9.4

Table 12.4.12.1.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	9.2 (0.27)	9.2 (0.32)	9.1 (0.29)	9.2 (0.27)	9.1 (0.28)	9.2 (0.29)
Visit 13/ET						
n/N2	56/56	33/33	59/60	27/29	115/116	60/62
Mean (SD)	9.4 (0.37)	9.3 (0.31)	9.4 (0.35)	9.2 (0.44)	9.4 (0.36)	9.3 (0.38)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.06)	0.3 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.16, 0.33]	[0.01, 0.23]	[0.21, 0.38]	[-0.07, 0.18]	[0.21, 0.33]	[0.00, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.24		0.19	
95% CI	[-0.01, 0.27]		[0.09, 0.39]		[0.09, 0.29]	
p-value	0.0643		0.0020		0.0003	
Hedges' g	0.47		0.74		0.60	
95% CI	[0.04, 0.90]		[0.28, 1.21]		[0.29, 0.92]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_1_m_dca_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0503		0.1855		0.6962	
Comparison Baseline vs. EAP	0.2681		0.3056		0.9477	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	3.8 (0.52)	3.9 (0.61)	3.8 (0.43)	3.7 (0.43)	3.8 (0.47)	3.8 (0.53)
Visit 13/ET						
n/N1	59/59	28/29	58/59	30/31	117/118	58/60
Mean (SD)	4.0 (0.65)	3.8 (0.55)	4.0 (0.57)	3.8 (0.73)	4.0 (0.61)	3.8 (0.64)
EAP						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	4.0 (0.60)	4.0 (0.54)	4.0 (0.47)	3.8 (0.55)	4.0 (0.54)	3.9 (0.55)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	-0.1 (0.09)	0.1 (0.07)	0.1 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.08, 0.34]	[-0.25, 0.12]	[-0.00, 0.28]	[-0.11, 0.28]	[0.08, 0.27]	[-0.12, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.28		0.05		0.17	
95% CI	[0.05, 0.50]		[-0.19, 0.29]		[0.00, 0.33]	
p-value	0.0158		0.6771		0.0455	
Hedges' g	0.54		0.04		0.28	
95% CI	[0.09, 1.00]		[-0.40, 0.48]		[-0.03, 0.59]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.05)
95% CI	[0.11, 0.30]	[-0.02, 0.24]	[0.06, 0.26]	[-0.04, 0.23]	[0.11, 0.25]	[0.01, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.06		0.07	
95% CI	[-0.07, 0.25]		[-0.11, 0.23]		[-0.04, 0.19]	
p-value	0.2682		0.4645		0.2219	
Hedges' g	0.26		0.08		0.17	
95% CI	[-0.18, 0.70]		[-0.36, 0.51]		[-0.14, 0.48]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	3.6 (0.55)	3.7 (0.58)	3.7 (0.68)	3.5 (0.43)	3.7 (0.62)	3.6 (0.52)
Visit 13/ET						
n/N2	56/56	33/33	59/60	27/29	115/116	60/62
Mean (SD)	3.7 (0.74)	3.9 (0.72)	4.1 (0.86)	3.6 (0.71)	3.9 (0.82)	3.8 (0.73)
EAP						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	3.7 (0.60)	3.9 (0.60)	4.1 (0.82)	3.6 (0.51)	3.9 (0.74)	3.8 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.4.14.1.s2.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.2 (0.11)	0.4 (0.09)	0.0 (0.13)	0.2 (0.06)	0.1 (0.08)
95% CI	[-0.05, 0.29]	[-0.01, 0.43]	[0.19, 0.54]	[-0.25, 0.26]	[0.12, 0.36]	[-0.06, 0.27]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.09		0.37		0.14	
95% CI	[-0.37, 0.18]		[0.05, 0.68]		[-0.06, 0.35]	
p-value	0.5010		0.0220		0.1739	
Hedges' g	-0.08		0.47		0.19	
95% CI	[-0.51, 0.35]		[0.01, 0.92]		[-0.12, 0.50]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.2 (0.08)	0.3 (0.07)	0.1 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[-0.04, 0.20]	[0.00, 0.31]	[0.20, 0.48]	[-0.12, 0.28]	[0.12, 0.30]	[-0.01, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.08		0.26		0.10	
95% CI	[-0.27, 0.12]		[0.01, 0.51]		[-0.06, 0.25]	
p-value	0.4398		0.0409		0.2127	
Hedges' g	-0.08		0.40		0.18	
95% CI	[-0.51, 0.34]		[-0.04, 0.84]		[-0.13, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_14_1_m_phos_sex_pp.sas using SAS 9.4

Table 12.5.1.1.1.s2.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3829		0.2230		0.3885	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	35/59	16/29	33/59	21/31	68/118	37/60
Mean (SD)	49.2 (39.35)	38.9 (39.01)	32.9 (21.31)	34.5 (28.30)	41.3 (32.71)	36.4 (32.92)
Visit 13/ET						
n/N1	34/59	5/29	31/59	14/31	65/118	19/60
Mean (SD)	49.6 (44.12)	29.2 (31.81)	54.3 (52.79)	72.0 (54.65)	51.8 (48.12)	60.7 (52.51)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	11.4 (8.00)	-12.6 (19.61)	22.9 (11.25)	39.0 (15.92)	17.2 (6.83)	13.0 (13.13)
95% CI	[-4.90, 27.71]	[-52.57, 27.32]	[-0.08, 45.89]	[6.50, 71.51]	[3.51, 30.81]	[-13.27, 39.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	24.03		-16.09		4.20	
95% CI	[-19.12, 67.19]		[-55.90, 23.72]		[-25.37, 33.78]	
p-value	0.2650		0.4156		0.7774	
Hedges' g	0.53		-0.30		-0.12	
95% CI	[-0.40, 1.47]		[-1.01, 0.41]		[-0.68, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_5_1_1_1_m_fgf23_sex_pp.sas using SAS 9.4

Table 12.5.1.1.1.s2.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	45/56	19/33	36/60	18/29	81/116	37/62
Mean (SD)	45.9 (62.91)	46.3 (32.80)	35.9 (28.64)	33.7 (23.35)	41.4 (50.61)	40.2 (28.92)
Visit 13/ET						
n/N2	35/56	17/33	36/60	11/29	71/116	28/62
Mean (SD)	47.4 (50.76)	46.1 (31.19)	67.6 (83.50)	52.2 (63.56)	57.6 (69.58)	48.5 (45.63)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.6 (8.48)	-5.5 (12.20)	44.0 (17.49)	16.7 (28.22)	20.5 (9.09)	4.5 (13.95)
95% CI	[-18.70, 15.52]	[-30.08, 19.11]	[8.38, 79.53]	[-40.73, 74.09]	[2.35, 38.56]	[-23.33, 32.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.89		27.27		15.99	
95% CI	[-26.07, 33.85]		[-40.30, 94.85]		[-17.17, 49.16]	
p-value	0.7947		0.4175		0.3399	
Hedges' g	0.04		0.33		0.20	
95% CI	[-0.57, 0.64]		[-0.39, 1.04]		[-0.27, 0.66]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_5_1_1_1_m_fgf23_sex_pp.sas using SAS 9.4

Table 12.4.12.1.2.s2.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7859		0.7624		0.6923	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	59/59	29/29	59/59	31/31	118/118	60/60
Mean (SD)	29.8 (10.57)	33.0 (11.64)	32.0 (10.53)	34.2 (9.80)	30.9 (10.56)	33.6 (10.65)
Visit 13/ET						
n/N1	59/59	28/29	58/59	30/31	117/118	58/60
Mean (SD)	30.2 (11.79)	33.3 (11.60)	30.7 (13.00)	32.9 (10.75)	30.5 (12.36)	33.1 (11.07)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.85)	0.0 (1.24)	-0.9 (0.89)	-1.1 (1.24)	-0.3 (0.62)	-0.6 (0.88)
95% CI	[-1.41, 1.98]	[-2.43, 2.51]	[-2.69, 0.85]	[-3.59, 1.35]	[-1.53, 0.91]	[-2.29, 1.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.25		0.20		0.25	
95% CI	[-2.77, 3.26]		[-2.85, 3.24]		[-1.88, 2.38]	
p-value	0.8718		0.8975		0.8176	
Hedges' g	0.09		0.02		0.06	
95% CI	[-0.35, 0.54]		[-0.41, 0.46]		[-0.25, 0.38]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_2_m_egfr_sex_pp.sas using SAS 9.4

Table 12.4.12.1.2.s2.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	56/56	33/33	60/60	29/29	116/116	62/62
Mean (SD)	30.8 (11.48)	33.6 (10.68)	29.6 (8.19)	30.7 (8.42)	30.2 (9.89)	32.2 (9.72)
Visit 13/ET						
n/N2	56/56	33/33	59/60	27/29	115/116	60/62
Mean (SD)	29.8 (11.91)	32.5 (11.45)	27.6 (9.03)	28.6 (10.24)	28.7 (10.54)	30.7 (11.00)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.3 (1.05)	-0.7 (1.37)	-1.8 (0.70)	-1.4 (1.04)	-1.5 (0.63)	-1.1 (0.88)
95% CI	[-3.36, 0.81]	[-3.47, 1.97]	[-3.20, -0.41]	[-3.45, 0.67]	[-2.77, -0.28]	[-2.83, 0.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.52		-0.42		-0.43	
95% CI	[-3.96, 2.92]		[-2.90, 2.07]		[-2.57, 1.71]	
p-value	0.7630		0.7394		0.6944	
Hedges' g	0.01		-0.07		-0.03	
95% CI	[-0.42, 0.43]		[-0.52, 0.38]		[-0.34, 0.28]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_12_1_2_m_egfr_sex_pp.sas using SAS 9.4

Table 12.4.15.1.1.s2.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4859		0.5106		0.3162	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
Baseline						
n/N1	46/59	21/29	38/59	20/31	84/118	41/60
Mean (SD)	0.6 (0.84)	0.6 (0.70)	0.6 (0.87)	0.6 (1.03)	0.6 (0.85)	0.6 (0.87)
Visit 13/ET						
n/N1	45/59	21/29	36/59	16/31	81/118	37/60
Mean (SD)	0.6 (1.13)	0.6 (0.78)	0.6 (0.75)	0.6 (0.74)	0.6 (0.98)	0.6 (0.75)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.10)	0.1 (0.15)	-0.1 (0.11)	-0.1 (0.17)	0.0 (0.08)	-0.0 (0.12)
95% CI	[-0.16, 0.24]	[-0.22, 0.37]	[-0.28, 0.17]	[-0.41, 0.28]	[-0.16, 0.16]	[-0.24, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.01		0.01	
95% CI	[-0.39, 0.32]		[-0.40, 0.42]		[-0.28, 0.29]	
p-value	0.8417		0.9659		0.9652	
Hedges' g	-0.05		0.06		-0.00	
95% CI	[-0.57, 0.46]		[-0.54, 0.66]		[-0.39, 0.39]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_15_1_1_m_ua_sex_pp.sas using SAS 9.4

Table 12.4.15.1.1.s2.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
Baseline						
n/N2	47/56	32/33	51/60	26/29	98/116	58/62
Mean (SD)	0.7 (0.74)	0.7 (1.10)	0.8 (1.03)	0.9 (1.36)	0.7 (0.90)	0.8 (1.21)
Visit 13/ET						
n/N2	48/56	33/33	50/60	23/29	98/116	56/62
Mean (SD)	0.8 (0.92)	0.7 (0.96)	1.0 (1.20)	0.6 (0.76)	0.9 (1.08)	0.7 (0.87)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.09)	-0.0 (0.11)	0.2 (0.10)	-0.0 (0.14)	0.2 (0.07)	-0.0 (0.09)
95% CI	[-0.09, 0.28]	[-0.25, 0.19]	[0.02, 0.41]	[-0.31, 0.25]	[0.02, 0.29]	[-0.21, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.24		0.18	
95% CI	[-0.17, 0.41]		[-0.10, 0.58]		[-0.04, 0.40]	
p-value	0.4068		0.1660		0.1000	
Hedges' g	0.19		0.32		0.26	
95% CI	[-0.25, 0.63]		[-0.17, 0.81]		[-0.07, 0.59]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_15_1_1_m_ua_sex_pp.sas using SAS 9.4

Table 12.4.12.1.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4463		0.1320		0.6011	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	9.1 (0.26)	9.3 (0.26)	9.2 (0.30)	9.3 (0.23)	9.2 (0.29)	9.3 (0.24)
Visit 13/ET						
n/N1	58/58	29/30	60/60	24/24	118/118	53/54
Mean (SD)	9.4 (0.43)	9.3 (0.32)	9.5 (0.36)	9.5 (0.56)	9.5 (0.40)	9.4 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.08)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.18, 0.37]	[-0.05, 0.22]	[0.19, 0.38]	[0.04, 0.34]	[0.22, 0.35]	[0.04, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.19		0.10		0.14	
95% CI	[0.02, 0.35]		[-0.08, 0.27]		[0.02, 0.26]	
p-value	0.0284		0.2832		0.0186	
Hedges' g	0.60		0.27		0.45	
95% CI	[0.15, 1.05]		[-0.20, 0.74]		[0.13, 0.78]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_1_m_dca_wt_pp.sas using SAS 9.4

Table 12.4.12.1.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	9.2 (0.28)	9.2 (0.29)	9.2 (0.33)	9.2 (0.30)	9.2 (0.31)	9.2 (0.30)
Visit 13/ET						
n/N2	57/57	32/32	57/59	33/36	114/116	65/68
Mean (SD)	9.5 (0.36)	9.4 (0.34)	9.5 (0.39)	9.3 (0.53)	9.5 (0.38)	9.3 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.3 (0.05)	0.0 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.18, 0.34]	[0.03, 0.25]	[0.22, 0.41]	[-0.08, 0.17]	[0.23, 0.35]	[0.01, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.27		0.19	
95% CI	[-0.01, 0.26]		[0.12, 0.42]		[0.09, 0.30]	
p-value	0.0784		0.0007		0.0002	
Hedges' g	0.36		0.76		0.57	
95% CI	[-0.07, 0.79]		[0.33, 1.20]		[0.26, 0.88]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_1_m_dca_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3628		0.9531		0.5374	
Comparison Baseline vs. EAP	0.1198		0.6030		0.1844	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	3.8 (0.59)	3.8 (0.63)	3.9 (0.58)	3.6 (0.38)	3.8 (0.58)	3.7 (0.54)
Visit 13/ET						
n/N1	58/58	29/30	60/60	24/24	118/118	53/54
Mean (SD)	4.0 (0.79)	3.9 (0.58)	4.0 (0.64)	3.6 (0.65)	4.0 (0.72)	3.8 (0.63)
EAP						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	4.0 (0.70)	4.0 (0.53)	4.1 (0.63)	3.6 (0.53)	4.0 (0.66)	3.8 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.08)	0.1 (0.11)	0.2 (0.07)	-0.1 (0.12)	0.2 (0.05)	0.0 (0.08)
95% CI	[0.11, 0.42]	[-0.13, 0.31]	[0.05, 0.34]	[-0.32, 0.14]	[0.12, 0.33]	[-0.15, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.28		0.22	
95% CI	[-0.09, 0.44]		[0.01, 0.56]		[0.03, 0.41]	
p-value	0.1989		0.0431		0.0225	
Hedges' g	0.31		0.31		0.30	
95% CI	[-0.13, 0.76]		[-0.17, 0.78]		[-0.02, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.3 (0.05)	0.1 (0.08)	0.2 (0.06)	-0.1 (0.10)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.15, 0.37]	[-0.01, 0.29]	[0.09, 0.33]	[-0.24, 0.14]	[0.15, 0.31]	[-0.07, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.26		0.18	
95% CI	[-0.07, 0.30]		[0.03, 0.49]		[0.03, 0.32]	
p-value	0.2158		0.0274		0.0155	
Hedges' g	0.31		0.39		0.33	
95% CI	[-0.13, 0.75]		[-0.09, 0.86]		[0.01, 0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	3.7 (0.49)	3.8 (0.56)	3.7 (0.56)	3.6 (0.48)	3.7 (0.52)	3.7 (0.52)
Visit 13/ET						
n/N2	57/57	32/32	57/59	33/36	114/116	65/68
Mean (SD)	3.8 (0.58)	3.8 (0.71)	4.0 (0.81)	3.8 (0.77)	3.9 (0.72)	3.8 (0.74)
EAP						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	3.7 (0.49)	3.9 (0.61)	4.0 (0.71)	3.8 (0.52)	3.9 (0.62)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.4.14.1.s3.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.1 (0.10)	0.3 (0.09)	0.1 (0.11)	0.2 (0.06)	0.1 (0.07)
95% CI	[-0.08, 0.20]	[-0.12, 0.26]	[0.15, 0.49]	[-0.09, 0.36]	[0.09, 0.31]	[-0.05, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.19		0.10	
95% CI	[-0.25, 0.23]		[-0.09, 0.47]		[-0.09, 0.28]	
p-value	0.9336		0.1817		0.3030	
Hedges' g	0.03		0.29		0.16	
95% CI	[-0.40, 0.45]		[-0.14, 0.71]		[-0.14, 0.47]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.0 (0.05)	0.1 (0.07)	0.3 (0.06)	0.2 (0.08)	0.2 (0.04)	0.2 (0.05)
95% CI	[-0.07, 0.13]	[-0.01, 0.26]	[0.17, 0.42]	[0.03, 0.34]	[0.08, 0.24]	[0.05, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.09		0.11		0.01	
95% CI	[-0.26, 0.08]		[-0.09, 0.31]		[-0.12, 0.14]	
p-value	0.2754		0.2606		0.8440	
Hedges' g	-0.18		0.22		0.03	
95% CI	[-0.61, 0.25]		[-0.19, 0.63]		[-0.26, 0.33]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_14_1_m_phos_wt_pp.sas using SAS 9.4

Table 12.5.1.1.1.s3.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1640		0.7157		0.5569	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	36/58	16/30	32/60	18/24	68/118	34/54
Mean (SD)	36.7 (24.08)	39.5 (38.09)	36.2 (30.08)	33.8 (28.97)	36.4 (26.87)	36.5 (33.17)
Visit 13/ET						
n/N1	35/58	7/30	36/60	8/24	71/118	15/54
Mean (SD)	51.5 (60.45)	38.2 (30.86)	56.6 (56.38)	74.3 (67.56)	54.0 (58.06)	57.5 (55.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	21.1 (11.36)	-12.9 (28.38)	26.1 (14.11)	36.7 (25.79)	23.5 (8.91)	13.2 (19.03)
95% CI	[-2.06, 44.30]	[-70.81, 44.94]	[-2.85, 55.04]	[-16.20, 89.64]	[5.68, 41.33]	[-24.90, 51.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	34.06		-10.62		10.33	
95% CI	[-29.06, 97.17]		[-71.28, 50.04]		[-32.05, 52.71]	
p-value	0.2796		0.7222		0.6274	
Hedges' g	0.67		-0.01		0.24	
95% CI	[-0.27, 1.61]		[-0.84, 0.81]		[-0.38, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_5_1_1_1_m_fgf23_wt_pp.sas using SAS 9.4

Table 12.5.1.1.1.s3.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	44/57	19/32	37/59	21/36	81/116	40/68
Mean (SD)	56.1 (68.07)	45.8 (33.80)	32.9 (20.52)	34.4 (23.47)	45.5 (53.05)	39.8 (29.04)
Visit 13/ET						
n/N2	34/57	15/32	31/59	17/36	65/116	32/68
Mean (SD)	45.4 (28.62)	44.2 (32.56)	67.1 (85.14)	58.1 (54.92)	55.7 (62.77)	51.6 (45.66)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-8.2 (5.25)	-9.2 (7.67)	42.2 (16.56)	23.7 (22.16)	16.3 (7.92)	6.3 (11.04)
95% CI	[-18.79, 2.36]	[-24.63, 6.30]	[8.59, 75.74]	[-21.27, 68.60]	[0.53, 32.03]	[-15.64, 28.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.95		18.50		9.95	
95% CI	[-17.81, 19.71]		[-37.73, 74.73]		[-17.11, 37.00]	
p-value	0.9190		0.5089		0.4666	
Hedges' g	-0.12		0.18		0.01	
95% CI	[-0.73, 0.48]		[-0.46, 0.82]		[-0.43, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_5_1_1_1_m_fgf23_wt_pp.sas using SAS 9.4

Table 12.4.12.1.2.s3.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4788		0.2410		0.1943	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	58/58	30/30	60/60	24/24	118/118	54/54
Mean (SD)	30.2 (10.62)	33.3 (11.95)	29.7 (8.82)	30.5 (8.41)	29.9 (9.70)	32.1 (10.54)
Visit 13/ET						
n/N1	58/58	29/30	60/60	24/24	118/118	53/54
Mean (SD)	28.9 (10.89)	33.0 (11.93)	27.6 (8.90)	29.5 (9.20)	28.2 (9.91)	31.4 (10.82)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.5 (0.81)	-0.5 (1.15)	-2.2 (0.61)	-0.9 (0.97)	-1.8 (0.51)	-0.7 (0.76)
95% CI	[-3.06, 0.16]	[-2.76, 1.80]	[-3.38, -0.94]	[-2.78, 1.08]	[-2.80, -0.81]	[-2.17, 0.83]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.97		-1.31		-1.13	
95% CI	[-3.78, 1.83]		[-3.60, 0.98]		[-2.94, 0.67]	
p-value	0.4920		0.2580		0.2174	
Hedges' g	-0.07		-0.25		-0.15	
95% CI	[-0.51, 0.37]		[-0.72, 0.22]		[-0.47, 0.17]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_2_m_egfr_wt_pp.sas using SAS 9.4

Table 12.4.12.1.2.s3.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	57/57	32/32	59/59	36/36	116/116	68/68
Mean (SD)	30.4 (11.45)	33.3 (10.32)	31.9 (10.02)	33.8 (9.64)	31.2 (10.72)	33.6 (9.89)
Visit 13/ET						
n/N2	57/57	32/32	57/59	33/36	114/116	65/68
Mean (SD)	31.1 (12.66)	32.7 (11.14)	30.8 (13.14)	31.8 (11.61)	31.0 (12.84)	32.3 (11.30)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.5 (1.08)	-0.3 (1.44)	-0.5 (0.93)	-1.6 (1.22)	0.0 (0.72)	-0.9 (0.96)
95% CI	[-1.65, 2.64]	[-3.13, 2.61]	[-2.36, 1.34]	[-4.01, 0.85]	[-1.42, 1.43]	[-2.82, 0.95]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.76		1.07		0.94	
95% CI	[-2.84, 4.36]		[-1.99, 4.14]		[-1.44, 3.31]	
p-value	0.6764		0.4879		0.4366	
Hedges' g	0.15		0.13		0.14	
95% CI	[-0.28, 0.58]		[-0.29, 0.56]		[-0.16, 0.45]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_12_1_2_m_egfr_wt_pp.sas using SAS 9.4

Table 12.4.15.1.1.s3.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8871		0.0574		0.2031	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
Baseline						
n/N1	49/58	26/30	44/60	19/24	93/118	45/54
Mean (SD)	0.6 (0.75)	0.6 (0.74)	0.7 (0.90)	0.6 (0.87)	0.6 (0.82)	0.6 (0.79)
Visit 13/ET						
n/N1	50/58	27/30	43/60	19/24	93/118	46/54
Mean (SD)	0.7 (1.17)	0.6 (0.88)	0.7 (0.87)	0.7 (0.81)	0.7 (1.04)	0.6 (0.84)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.09)	0.1 (0.13)	0.0 (0.10)	0.1 (0.14)	0.1 (0.07)	0.1 (0.10)
95% CI	[-0.06, 0.31]	[-0.18, 0.33]	[-0.15, 0.23]	[-0.14, 0.42]	[-0.06, 0.22]	[-0.09, 0.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		-0.10		-0.03	
95% CI	[-0.27, 0.37]		[-0.44, 0.24]		[-0.27, 0.21]	
p-value	0.7491		0.5731		0.8116	
Hedges' g	0.10		-0.22		-0.04	
95% CI	[-0.36, 0.56]		[-0.76, 0.32]		[-0.39, 0.32]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_15_1_1_m_ua_wt_pp.sas using SAS 9.4

Table 12.4.15.1.1.s3.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
Baseline						
n/N2	44/57	27/32	45/59	27/36	89/116	54/68
Mean (SD)	0.7 (0.83)	0.8 (1.13)	0.8 (1.02)	0.9 (1.43)	0.7 (0.93)	0.9 (1.28)
Visit 13/ET						
n/N2	43/57	27/32	43/59	20/36	86/116	47/68
Mean (SD)	0.7 (0.84)	0.7 (0.90)	0.9 (1.21)	0.5 (0.69)	0.8 (1.04)	0.7 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.09)	-0.0 (0.11)	0.2 (0.12)	-0.3 (0.18)	0.1 (0.07)	-0.1 (0.10)
95% CI	[-0.19, 0.16]	[-0.24, 0.20]	[-0.07, 0.42]	[-0.62, 0.11]	[-0.07, 0.23]	[-0.34, 0.07]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.00		0.43		0.22	
95% CI	[-0.28, 0.29]		[-0.01, 0.87]		[-0.03, 0.47]	
p-value	0.9760		0.0536		0.0886	
Hedges' g	0.05		0.52		0.29	
95% CI	[-0.43, 0.53]		[-0.02, 1.07]		[-0.07, 0.65]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_15_1_1_m_ua_wt_pp.sas using SAS 9.4

Table 12.4.12.1.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5301		0.0034		0.0124	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	9.2 (0.26)	9.2 (0.29)	9.2 (0.32)	9.2 (0.28)	9.2 (0.29)	9.2 (0.29)
Visit 13/ET						
n/N1	65/65	41/41	82/83	39/39	147/148	80/80
Mean (SD)	9.4 (0.40)	9.3 (0.36)	9.6 (0.36)	9.3 (0.52)	9.5 (0.38)	9.3 (0.44)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.05)	0.3 (0.04)	0.0 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.20, 0.36]	[0.00, 0.21]	[0.26, 0.41]	[-0.08, 0.14]	[0.25, 0.36]	[-0.01, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.31		0.24	
95% CI	[0.05, 0.31]		[0.18, 0.44]		[0.15, 0.34]	
p-value	0.0082		<0.0001		<0.0001	
Hedges' g	0.57		0.87		0.73	
95% CI	[0.17, 0.96]		[0.47, 1.26]		[0.45, 1.01]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_1_m_dca_race_pp.sas using SAS 9.4

Table 12.4.12.1.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	9.2 (0.29)	9.3 (0.24)	9.2 (0.32)	9.3 (0.26)	9.2 (0.30)	9.3 (0.25)
Visit 13/ET						
n/N2	50/50	20/21	35/36	18/21	85/86	38/42
Mean (SD)	9.5 (0.41)	9.4 (0.23)	9.5 (0.41)	9.5 (0.58)	9.5 (0.41)	9.5 (0.43)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.08)	0.2 (0.06)	0.3 (0.08)	0.2 (0.04)	0.2 (0.06)
95% CI	[0.15, 0.34]	[-0.01, 0.30]	[0.10, 0.34]	[0.11, 0.44]	[0.15, 0.31]	[0.09, 0.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.05		0.03	
95% CI	[-0.08, 0.28]		[-0.26, 0.15]		[-0.11, 0.17]	
p-value	0.2773		0.5937		0.6942	
Hedges' g	0.36		-0.16		0.13	
95% CI	[-0.16, 0.88]		[-0.72, 0.40]		[-0.25, 0.51]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_1_m_dca_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.9840		0.0826		0.1850	
Comparison Baseline vs. EAP	0.9950		0.1392		0.2283	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	3.7 (0.57)	3.8 (0.60)	3.8 (0.56)	3.6 (0.39)	3.7 (0.56)	3.7 (0.51)
Visit 13/ET						
n/N1	65/65	41/41	82/83	39/39	147/148	80/80
Mean (SD)	3.9 (0.71)	3.9 (0.69)	4.0 (0.74)	3.6 (0.67)	4.0 (0.73)	3.8 (0.69)
EAP						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	3.9 (0.63)	3.9 (0.61)	4.0 (0.68)	3.7 (0.50)	3.9 (0.66)	3.8 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.09)	0.3 (0.07)	-0.0 (0.10)	0.2 (0.05)	0.0 (0.07)
95% CI	[0.03, 0.32]	[-0.09, 0.28]	[0.14, 0.40]	[-0.23, 0.15]	[0.13, 0.32]	[-0.11, 0.15]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.31		0.20	
95% CI	[-0.15, 0.32]		[0.08, 0.55]		[0.04, 0.37]	
p-value	0.4913		0.0086		0.0143	
Hedges' g	0.18		0.47		0.33	
95% CI	[-0.21, 0.57]		[0.09, 0.85]		[0.06, 0.60]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.3 (0.05)	0.0 (0.07)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.04, 0.25]	[0.00, 0.27]	[0.15, 0.35]	[-0.12, 0.17]	[0.13, 0.27]	[-0.02, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.23		0.12	
95% CI	[-0.16, 0.18]		[0.05, 0.40]		[0.00, 0.24]	
p-value	0.9078		0.0126		0.0499	
Hedges' g	0.07		0.45		0.27	
95% CI	[-0.32, 0.46]		[0.07, 0.83]		[-0.00, 0.54]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	3.7 (0.50)	3.8 (0.59)	3.8 (0.60)	3.6 (0.54)	3.8 (0.55)	3.7 (0.56)
Visit 13/ET						
n/N2	50/50	20/21	35/36	18/21	85/86	38/42
Mean (SD)	3.9 (0.71)	3.8 (0.56)	4.0 (0.69)	3.9 (0.80)	3.9 (0.70)	3.9 (0.68)
EAP						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	3.9 (0.61)	3.9 (0.50)	4.1 (0.65)	3.9 (0.57)	3.9 (0.63)	3.9 (0.53)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.4.14.1.s4.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.1 (0.12)	0.2 (0.10)	0.2 (0.15)	0.2 (0.06)	0.2 (0.09)
95% CI	[0.00, 0.31]	[-0.18, 0.30]	[0.01, 0.43]	[-0.05, 0.54]	[0.06, 0.31]	[-0.03, 0.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		-0.02		0.03	
95% CI	[-0.19, 0.38]		[-0.39, 0.34]		[-0.19, 0.26]	
p-value	0.5066		0.8924		0.7806	
Hedges' g	0.18		-0.13		0.01	
95% CI	[-0.34, 0.69]		[-0.69, 0.43]		[-0.37, 0.39]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.08)	0.2 (0.08)	0.2 (0.11)	0.2 (0.05)	0.2 (0.07)
95% CI	[0.04, 0.25]	[-0.04, 0.29]	[0.08, 0.42]	[-0.02, 0.42]	[0.10, 0.29]	[0.04, 0.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.05		0.02	
95% CI	[-0.18, 0.22]		[-0.23, 0.33]		[-0.14, 0.19]	
p-value	0.8463		0.7234		0.7903	
Hedges' g	0.07		-0.05		-0.01	
95% CI	[-0.43, 0.57]		[-0.58, 0.49]		[-0.38, 0.36]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_14_1_m_phos_race_pp.sas using SAS 9.4

Table 12.5.1.1.1.s4.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6076		0.7033		0.8725	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	46/65	21/41	44/83	24/39	90/148	45/80
Mean (SD)	54.8 (66.49)	49.0 (38.13)	34.2 (26.89)	32.2 (22.98)	44.7 (51.89)	40.1 (31.76)
Visit 13/ET						
n/N1	39/65	16/41	47/83	11/39	86/148	27/80
Mean (SD)	52.7 (54.02)	41.6 (30.84)	60.5 (71.12)	61.5 (72.59)	57.0 (63.70)	49.7 (51.71)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	1.5 (8.31)	-11.9 (13.34)	33.0 (13.99)	28.3 (25.45)	16.8 (7.89)	7.4 (13.57)
95% CI	[-15.23, 18.22]	[-38.74, 14.94]	[4.71, 61.27]	[-23.15, 79.72]	[1.11, 32.47]	[-19.62, 34.32]
Diff in LS-Mean [ER-Calcifediol - Placebo]	13.40		4.70		9.44	
95% CI	[-18.24, 45.04]		[-54.05, 63.45]		[-21.76, 40.64]	
p-value	0.3987		0.8723		0.5493	
Hedges' g	0.10		0.02		0.09	
95% CI	[-0.51, 0.71]		[-0.67, 0.72]		[-0.37, 0.55]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_5_1_1_1_m_fgf23_race_pp.sas using SAS 9.4

Table 12.5.1.1.1.s4.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	34/50	14/21	25/36	15/21	59/86	29/42
Mean (SD)	37.2 (25.84)	33.8 (29.91)	34.9 (22.64)	37.1 (30.39)	36.2 (24.36)	35.5 (29.66)
Visit 13/ET						
n/N2	30/50	6/21	20/36	14/21	50/86	20/42
Mean (SD)	43.0 (36.88)	44.1 (35.89)	63.6 (71.72)	64.7 (47.14)	51.2 (53.89)	58.5 (44.20)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.9 (7.87)	6.3 (16.40)	37.6 (18.20)	28.0 (21.30)	23.2 (9.00)	16.9 (14.14)
95% CI	[-7.22, 25.04]	[-27.34, 39.86]	[-0.09, 75.19]	[-16.06, 72.05]	[5.19, 41.29]	[-11.52, 45.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	2.65		9.56		6.39	
95% CI	[-35.00, 40.30]		[-48.79, 67.90]		[-27.55, 40.33]	
p-value	0.8865		0.7378		0.7072	
Hedges' g	0.38		0.22		0.15	
95% CI	[-0.49, 1.25]		[-0.53, 0.98]		[-0.41, 0.71]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_5_1_1_1_m_fgf23_race_pp.sas using SAS 9.4

Table 12.4.12.1.2.s4.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0364		0.0047		0.0005	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	65/65	41/41	83/83	39/39	148/148	80/80
Mean (SD)	28.5 (9.49)	32.3 (11.08)	30.2 (9.12)	30.4 (8.28)	29.5 (9.29)	31.4 (9.80)
Visit 13/ET						
n/N1	65/65	41/41	82/83	39/39	147/148	80/80
Mean (SD)	27.3 (9.45)	32.7 (12.14)	27.8 (9.67)	30.3 (10.86)	27.6 (9.54)	31.5 (11.53)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.4 (0.78)	0.8 (0.98)	-2.2 (0.53)	-0.1 (0.77)	-1.8 (0.46)	0.3 (0.62)
95% CI	[-2.96, 0.13]	[-1.17, 2.74]	[-3.29, -1.19]	[-1.63, 1.42]	[-2.69, -0.87]	[-0.97, 1.49]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-2.20		-2.14		-2.04	
95% CI	[-4.71, 0.31]		[-3.99, -0.29]		[-3.57, -0.50]	
p-value	0.0853		0.0237		0.0094	
Hedges' g	-0.25		-0.45		-0.35	
95% CI	[-0.64, 0.14]		[-0.83, -0.06]		[-0.62, -0.07]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_2_m_egfr_race_pp.sas using SAS 9.4

Table 12.4.12.1.2.s4.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	50/50	21/21	36/36	21/21	86/86	42/42
Mean (SD)	32.7 (12.37)	35.3 (10.99)	32.1 (10.21)	36.4 (9.85)	32.4 (11.45)	35.9 (10.32)
Visit 13/ET						
n/N2	50/50	20/21	35/36	18/21	85/86	38/42
Mean (SD)	33.5 (13.59)	33.1 (10.10)	32.2 (13.95)	32.2 (10.30)	33.0 (13.67)	32.7 (10.07)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.7 (1.18)	-2.5 (1.87)	0.7 (1.37)	-3.7 (1.92)	0.6 (0.91)	-3.0 (1.35)
95% CI	[-1.69, 3.01]	[-6.28, 1.19]	[-2.05, 3.45]	[-7.61, 0.12]	[-1.20, 2.41]	[-5.72, -0.37]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.20		4.45		3.66	
95% CI	[-1.23, 7.63]		[-0.34, 9.24]		[0.41, 6.90]	
p-value	0.1536		0.0681		0.0275	
Hedges' g	0.44		0.55		0.50	
95% CI	[-0.07, 0.96]		[-0.02, 1.11]		[0.11, 0.88]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_12_1_2_m_egfr_race_pp.sas using SAS 9.4

Table 12.4.15.1.1.s4.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7945		0.5692		0.8207	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
Baseline						
n/N1	50/65	36/41	62/83	30/39	112/148	66/80
Mean (SD)	0.6 (0.83)	0.7 (0.91)	0.7 (0.97)	0.7 (1.11)	0.7 (0.91)	0.7 (1.00)
Visit 13/ET						
n/N1	51/65	39/41	59/83	26/39	110/148	65/80
Mean (SD)	0.6 (0.87)	0.6 (0.85)	0.8 (1.11)	0.7 (0.78)	0.7 (1.01)	0.6 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.08)	-0.0 (0.10)	0.1 (0.09)	-0.1 (0.13)	0.1 (0.06)	-0.0 (0.08)
95% CI	[-0.18, 0.15]	[-0.21, 0.18]	[-0.06, 0.29]	[-0.34, 0.19]	[-0.07, 0.17]	[-0.21, 0.11]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		0.19		0.10	
95% CI	[-0.26, 0.25]		[-0.12, 0.51]		[-0.10, 0.30]	
p-value	0.9949		0.2294		0.3425	
Hedges' g	0.01		0.28		0.15	
95% CI	[-0.41, 0.42]		[-0.18, 0.75]		[-0.16, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_15_1_1_m_ua_race_pp.sas using SAS 9.4

Table 12.4.15.1.1.s4.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
Baseline						
n/N2	43/50	17/21	27/36	16/21	70/86	33/42
Mean (SD)	0.6 (0.75)	0.7 (1.08)	0.8 (0.95)	1.0 (1.44)	0.7 (0.83)	0.8 (1.25)
Visit 13/ET						
n/N2	42/50	15/21	27/36	13/21	69/86	28/42
Mean (SD)	0.8 (1.18)	0.7 (1.00)	0.8 (0.95)	0.5 (0.69)	0.8 (1.09)	0.7 (0.86)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.11)	0.1 (0.18)	0.1 (0.15)	-0.1 (0.22)	0.1 (0.10)	0.0 (0.15)
95% CI	[-0.05, 0.38]	[-0.27, 0.46]	[-0.20, 0.43]	[-0.50, 0.39]	[-0.06, 0.32]	[-0.25, 0.34]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.07		0.17		0.08	
95% CI	[-0.35, 0.50]		[-0.38, 0.72]		[-0.27, 0.43]	
p-value	0.7329		0.5328		0.6415	
Hedges' g	0.10		0.05		0.09	
95% CI	[-0.48, 0.69]		[-0.60, 0.70]		[-0.35, 0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_15_1_1_m_ua_race_pp.sas using SAS 9.4

Table 12.4.12.1.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2737		0.0378		0.5085	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	9.2 (0.28)	9.3 (0.26)	9.3 (0.33)	9.3 (0.25)	9.2 (0.30)	9.3 (0.26)
Visit 13/ET						
n/N1	58/58	33/33	63/65	26/29	121/123	59/62
Mean (SD)	9.5 (0.41)	9.3 (0.29)	9.5 (0.37)	9.5 (0.50)	9.5 (0.39)	9.4 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.3 (0.04)	0.2 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.18, 0.36]	[-0.05, 0.19]	[0.20, 0.36]	[0.11, 0.35]	[0.21, 0.33]	[0.06, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.05		0.13	
95% CI	[0.05, 0.35]		[-0.10, 0.19]		[0.02, 0.23]	
p-value	0.0087		0.5333		0.0161	
Hedges' g	0.64		0.15		0.44	
95% CI	[0.20, 1.07]		[-0.30, 0.60]		[0.12, 0.75]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_1_m_dca_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	9.1 (0.27)	9.2 (0.28)	9.2 (0.30)	9.2 (0.30)	9.2 (0.29)	9.2 (0.29)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	9.4 (0.39)	9.3 (0.37)	9.5 (0.38)	9.2 (0.57)	9.5 (0.39)	9.3 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.2 (0.06)	0.3 (0.05)	0.0 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.18, 0.35]	[0.05, 0.30]	[0.22, 0.44]	[-0.14, 0.14]	[0.23, 0.36]	[-0.00, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.33		0.21	
95% CI	[-0.06, 0.24]		[0.15, 0.50]		[0.09, 0.32]	
p-value	0.2360		0.0004		0.0004	
Hedges' g	0.29		0.83		0.59	
95% CI	[-0.16, 0.74]		[0.38, 1.29]		[0.27, 0.91]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_1_m_dca_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.2405		0.7860		0.2967	
Comparison Baseline vs. EAP	0.9006		0.2885		0.3629	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	3.5 (0.49)	3.7 (0.57)	3.6 (0.54)	3.5 (0.42)	3.6 (0.52)	3.6 (0.50)
Visit 13/ET						
n/N1	58/58	33/33	63/65	26/29	121/123	59/62
Mean (SD)	3.6 (0.60)	3.8 (0.61)	3.7 (0.59)	3.6 (0.70)	3.7 (0.60)	3.7 (0.66)
EAP						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	3.6 (0.51)	3.8 (0.54)	3.7 (0.46)	3.6 (0.47)	3.7 (0.49)	3.7 (0.52)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.2 (0.09)	0.1 (0.06)	-0.0 (0.10)	0.1 (0.05)	0.1 (0.07)
95% CI	[-0.03, 0.23]	[-0.01, 0.34]	[0.00, 0.26]	[-0.22, 0.18]	[0.03, 0.21]	[-0.06, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.07		0.15		0.05	
95% CI	[-0.29, 0.15]		[-0.08, 0.39]		[-0.11, 0.20]	
p-value	0.5457		0.1996		0.5781	
Hedges' g	-0.02		0.25		0.10	
95% CI	[-0.44, 0.41]		[-0.20, 0.71]		[-0.21, 0.41]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.1 (0.04)	0.1 (0.06)	0.1 (0.03)	0.1 (0.05)
95% CI	[0.01, 0.21]	[0.01, 0.28]	[0.04, 0.20]	[-0.07, 0.18]	[0.05, 0.18]	[0.01, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.06		0.01	
95% CI	[-0.20, 0.14]		[-0.09, 0.21]		[-0.10, 0.12]	
p-value	0.7073		0.4009		0.8333	
Hedges' g	0.05		0.10		0.07	
95% CI	[-0.38, 0.47]		[-0.33, 0.53]		[-0.24, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	3.9 (0.51)	3.9 (0.60)	4.0 (0.54)	3.7 (0.45)	4.0 (0.53)	3.8 (0.54)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	4.2 (0.72)	3.9 (0.70)	4.4 (0.73)	3.9 (0.72)	4.3 (0.73)	3.9 (0.71)
EAP						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	4.1 (0.64)	4.1 (0.58)	4.4 (0.71)	3.9 (0.57)	4.2 (0.68)	4.0 (0.58)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.4.14.1.s5.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	-0.0 (0.12)	0.4 (0.09)	0.1 (0.12)	0.3 (0.06)	0.0 (0.08)
95% CI	[0.06, 0.39]	[-0.25, 0.22]	[0.23, 0.60]	[-0.17, 0.32]	[0.20, 0.44]	[-0.14, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.24		0.34		0.29	
95% CI	[-0.05, 0.53]		[0.03, 0.65]		[0.08, 0.50]	
p-value	0.0971		0.0302		0.0060	
Hedges' g	0.35		0.34		0.34	
95% CI	[-0.10, 0.80]		[-0.10, 0.78]		[0.02, 0.66]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.4 (0.07)	0.1 (0.10)	0.3 (0.05)	0.1 (0.06)
95% CI	[0.06, 0.29]	[-0.03, 0.29]	[0.27, 0.57]	[-0.10, 0.30]	[0.20, 0.39]	[-0.00, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.32		0.17	
95% CI	[-0.16, 0.24]		[0.06, 0.57]		[0.02, 0.33]	
p-value	0.6966		0.0144		0.0314	
Hedges' g	0.09		0.44		0.27	
95% CI	[-0.36, 0.53]		[-0.01, 0.88]		[-0.04, 0.59]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_14_1_m_phos_ckd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s5.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4808		0.1544		0.1539	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	33/58	14/33	33/65	17/29	66/123	31/62
Mean (SD)	43.8 (32.59)	42.1 (40.04)	34.9 (30.28)	30.7 (20.06)	39.3 (31.54)	35.8 (30.71)
Visit 13/ET						
n/N1	29/58	10/33	28/65	9/29	57/123	19/62
Mean (SD)	32.3 (22.64)	38.9 (32.80)	36.3 (20.77)	62.2 (46.65)	34.3 (21.64)	49.9 (40.58)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-6.3 (5.42)	-3.0 (8.99)	-1.9 (7.41)	19.6 (11.88)	-4.2 (4.58)	8.4 (7.45)
95% CI	[-17.44, 4.80]	[-21.41, 15.49]	[-17.28, 13.45]	[-5.02, 44.27]	[-13.35, 5.04]	[-6.54, 23.40]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-3.36		-21.54		-12.59	
95% CI	[-24.90, 18.18]		[-50.59, 7.50]		[-30.16, 4.98]	
p-value	0.7514		0.1383		0.1562	
Hedges' g	-0.10		-0.45		-0.30	
95% CI	[-0.89, 0.69]		[-1.31, 0.40]		[-0.89, 0.28]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_5_1_1_1_m_fgf23_ckd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s5.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	47/57	21/29	36/54	22/31	83/111	43/60
Mean (SD)	49.8 (64.66)	43.5 (33.02)	34.0 (20.03)	36.8 (29.68)	43.0 (50.78)	40.0 (31.16)
Visit 13/ET						
n/N2	40/57	12/29	39/54	16/31	79/111	28/60
Mean (SD)	60.1 (56.52)	45.1 (31.40)	79.5 (87.13)	63.9 (65.44)	69.7 (73.42)	55.8 (53.58)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	9.9 (8.43)	-6.4 (15.20)	57.2 (15.60)	30.2 (22.86)	32.7 (8.59)	12.3 (13.91)
95% CI	[-7.03, 26.88]	[-36.98, 24.16]	[25.73, 88.74]	[-15.98, 76.35]	[15.63, 49.75]	[-15.39, 39.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	16.33		27.05		20.44	
95% CI	[-18.63, 51.30]		[-28.91, 83.01]		[-12.06, 52.94]	
p-value	0.3523		0.3347		0.2147	
Hedges' g	0.27		0.32		0.23	
95% CI	[-0.37, 0.91]		[-0.31, 0.94]		[-0.22, 0.68]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_5_1_1_1_m_fgf23_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s5.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7676		0.9941		0.8592	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	58/58	33/33	65/65	29/29	123/123	62/62
Mean (SD)	38.2 (9.31)	40.5 (9.63)	37.3 (7.34)	39.4 (7.72)	37.7 (8.30)	40.0 (8.73)
Visit 13/ET						
n/N1	58/58	33/33	63/65	26/29	121/123	59/62
Mean (SD)	37.6 (9.74)	39.2 (9.73)	36.4 (9.93)	39.2 (8.15)	37.0 (9.82)	39.2 (8.99)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.8 (0.96)	-0.8 (1.28)	-0.7 (0.90)	-0.0 (1.41)	-0.8 (0.66)	-0.4 (0.95)
95% CI	[-2.76, 1.07]	[-3.39, 1.70]	[-2.52, 1.06]	[-2.83, 2.77]	[-2.10, 0.50]	[-2.28, 1.48]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.00		-0.70		-0.40	
95% CI	[-3.20, 3.19]		[-4.04, 2.64]		[-2.70, 1.89]	
p-value	0.9980		0.6787		0.7296	
Hedges' g	0.09		-0.04		0.03	
95% CI	[-0.33, 0.51]		[-0.50, 0.41]		[-0.28, 0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_2_m_egfr_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s5.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	57/57	29/29	54/54	31/31	111/111	60/60
Mean (SD)	22.3 (5.36)	25.2 (5.64)	22.9 (4.36)	26.0 (4.67)	22.6 (4.89)	25.6 (5.13)
Visit 13/ET						
n/N2	57/57	28/29	54/54	31/31	111/111	59/60
Mean (SD)	22.3 (8.20)	25.4 (8.51)	20.7 (5.11)	23.9 (6.83)	21.5 (6.89)	24.6 (7.64)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.2 (0.93)	0.3 (1.34)	-2.4 (0.63)	-1.7 (0.84)	-1.3 (0.56)	-0.7 (0.78)
95% CI	[-2.02, 1.68]	[-2.36, 2.98]	[-3.68, -1.20]	[-3.35, -0.02]	[-2.41, -0.19]	[-2.24, 0.85]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.48		-0.75		-0.61	
95% CI	[-3.77, 2.82]		[-2.88, 1.37]		[-2.54, 1.33]	
p-value	0.7733		0.4829		0.5362	
Hedges' g	-0.00		-0.05		-0.01	
95% CI	[-0.45, 0.45]		[-0.48, 0.39]		[-0.32, 0.31]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_12_1_2_m_egfr_ckd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s5.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.7505		0.3031		0.3654	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
Baseline						
n/N1	42/58	26/33	43/65	17/29	85/123	43/62
Mean (SD)	0.5 (0.65)	0.4 (0.87)	0.6 (0.93)	0.8 (1.44)	0.5 (0.80)	0.6 (1.13)
Visit 13/ET						
n/N1	43/58	27/33	44/65	17/29	87/123	44/62
Mean (SD)	0.5 (0.77)	0.5 (0.99)	0.7 (0.99)	0.6 (0.77)	0.6 (0.89)	0.6 (0.90)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.10)	0.1 (0.11)	0.1 (0.18)	0.1 (0.07)	0.1 (0.10)
95% CI	[-0.08, 0.24]	[-0.13, 0.26]	[-0.09, 0.36]	[-0.21, 0.51]	[-0.03, 0.24]	[-0.08, 0.30]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		-0.01		-0.00	
95% CI	[-0.24, 0.26]		[-0.44, 0.41]		[-0.24, 0.23]	
p-value	0.9178		0.9573		0.9867	
Hedges' g	0.02		-0.04		0.00	
95% CI	[-0.46, 0.50]		[-0.61, 0.53]		[-0.36, 0.37]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_15_1_1_m_ua_ckd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s5.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
Baseline						
n/N2	51/57	27/29	46/54	29/31	97/111	56/60
Mean (SD)	0.8 (0.86)	0.9 (0.99)	0.8 (0.98)	0.8 (1.11)	0.8 (0.92)	0.9 (1.04)
Visit 13/ET						
n/N2	50/57	27/29	42/54	22/31	92/111	49/60
Mean (SD)	0.9 (1.19)	0.8 (0.75)	1.0 (1.11)	0.6 (0.74)	0.9 (1.15)	0.7 (0.74)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.11)	-0.0 (0.15)	0.1 (0.11)	-0.2 (0.15)	0.1 (0.08)	-0.1 (0.11)
95% CI	[-0.16, 0.28]	[-0.33, 0.26]	[-0.13, 0.30]	[-0.52, 0.09]	[-0.08, 0.22]	[-0.33, 0.09]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.30		0.19	
95% CI	[-0.27, 0.46]		[-0.07, 0.67]		[-0.07, 0.45]	
p-value	0.6134		0.1105		0.1440	
Hedges' g	0.13		0.36		0.23	
95% CI	[-0.33, 0.59]		[-0.16, 0.87]		[-0.11, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
CKD: Chronic Kidney Disease
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_15_1_1_m_ua_ckd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4848		0.6576		0.3449	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	9.3 (0.25)	9.2 (0.27)	9.3 (0.28)	9.2 (0.31)	9.3 (0.27)	9.2 (0.28)
Visit 13/ET						
n/N1	36/36	23/23	46/48	16/16	82/84	39/39
Mean (SD)	9.5 (0.39)	9.3 (0.35)	9.6 (0.33)	9.4 (0.64)	9.6 (0.36)	9.4 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.3 (0.05)	0.2 (0.08)	0.3 (0.04)	0.1 (0.05)
95% CI	[0.10, 0.31]	[-0.04, 0.23]	[0.20, 0.39]	[0.02, 0.34]	[0.18, 0.32]	[0.03, 0.24]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.12		0.12	
95% CI	[-0.06, 0.29]		[-0.07, 0.30]		[-0.01, 0.24]	
p-value	0.2009		0.2149		0.0688	
Hedges' g	0.31		0.37		0.38	
95% CI	[-0.21, 0.83]		[-0.20, 0.93]		[-0.00, 0.76]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_1_m_dca_ttlpth_pp.sas using SAS 9.4

Table 12.4.12.1.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	9.2 (0.26)	9.2 (0.30)	9.3 (0.38)	9.3 (0.23)	9.2 (0.32)	9.3 (0.27)
Visit 13/ET						
n/N2	42/42	22/22	37/37	22/23	79/79	44/45
Mean (SD)	9.4 (0.42)	9.3 (0.31)	9.5 (0.37)	9.4 (0.40)	9.4 (0.40)	9.3 (0.36)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.05)	0.1 (0.07)	0.2 (0.06)	0.1 (0.07)	0.2 (0.04)	0.1 (0.05)
95% CI	[0.08, 0.29]	[-0.08, 0.21]	[0.13, 0.35]	[-0.05, 0.24]	[0.14, 0.29]	[-0.02, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.12		0.15		0.13	
95% CI	[-0.06, 0.30]		[-0.03, 0.33]		[0.00, 0.26]	
p-value	0.1993		0.1096		0.0419	
Hedges' g	0.38		0.45		0.42	
95% CI	[-0.13, 0.89]		[-0.08, 0.97]		[0.05, 0.79]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_1_m_dca_ttlpth_pp.sas using SAS 9.4

Table 12.4.12.1.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	9.1 (0.29)	9.2 (0.26)	9.1 (0.25)	9.2 (0.30)	9.1 (0.27)	9.2 (0.28)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	9.5 (0.39)	9.4 (0.32)	9.5 (0.43)	9.3 (0.64)	9.5 (0.41)	9.3 (0.51)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.05)	0.2 (0.08)	0.4 (0.07)	0.1 (0.09)	0.4 (0.04)	0.1 (0.06)
95% CI	[0.31, 0.53]		[0.23, 0.51]		[0.31, 0.48]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.21		0.32		0.27	
95% CI	[0.02, 0.41]		[0.08, 0.56]		[0.11, 0.42]	
p-value	0.0330		0.0102		0.0010	
Hedges' g	0.77		0.72		0.76	
95% CI	[0.17, 1.36]		[0.15, 1.29]		[0.35, 1.18]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_1_m_dca_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5097		0.7634		0.9365	
Comparison Baseline vs. EAP	0.0523		0.6627		0.5763	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	3.6 (0.50)	3.6 (0.55)	3.7 (0.52)	3.4 (0.46)	3.6 (0.51)	3.6 (0.52)
Visit 13/ET						
n/N1	36/36	23/23	46/48	16/16	82/84	39/39
Mean (SD)	3.7 (0.57)	3.8 (0.70)	3.9 (0.63)	3.5 (0.48)	3.8 (0.61)	3.7 (0.64)
EAP						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	3.7 (0.54)	3.9 (0.57)	3.9 (0.58)	3.6 (0.42)	3.8 (0.57)	3.7 (0.53)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.09)	0.2 (0.12)	0.3 (0.07)	-0.0 (0.12)	0.2 (0.06)	0.1 (0.08)
95% CI	[-0.05, 0.32]	[-0.06, 0.41]	[0.13, 0.41]	[-0.25, 0.24]	[0.09, 0.32]	[-0.09, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.04		0.28		0.13	
95% CI	[-0.34, 0.26]		[-0.01, 0.56]		[-0.07, 0.33]	
p-value	0.7940		0.0549		0.2097	
Hedges' g	-0.03		0.41		0.17	
95% CI	[-0.54, 0.49]		[-0.15, 0.98]		[-0.21, 0.55]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.2 (0.08)	0.3 (0.05)	0.1 (0.09)	0.2 (0.04)	0.2 (0.06)
95% CI	[-0.03, 0.24]	[0.05, 0.38]	[0.16, 0.37]	[-0.07, 0.30]	[0.10, 0.27]	[0.04, 0.28]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.11		0.15		0.02	
95% CI	[-0.32, 0.10]		[-0.06, 0.36]		[-0.12, 0.17]	
p-value	0.2967		0.1642		0.7543	
Hedges' g	-0.24		0.29		0.02	
95% CI	[-0.75, 0.28]		[-0.27, 0.85]		[-0.35, 0.40]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	3.7 (0.56)	3.9 (0.51)	3.8 (0.62)	3.8 (0.44)	3.7 (0.58)	3.8 (0.47)
Visit 13/ET						
n/N2	42/42	22/22	37/37	22/23	79/79	44/45
Mean (SD)	4.0 (0.72)	3.9 (0.67)	4.0 (0.73)	3.9 (0.91)	4.0 (0.72)	3.9 (0.79)
EAP						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	4.0 (0.58)	3.9 (0.56)	3.9 (0.59)	3.9 (0.64)	4.0 (0.58)	3.9 (0.60)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.09)	0.0 (0.12)	0.2 (0.11)	0.1 (0.14)	0.2 (0.07)	0.1 (0.09)
95% CI	[0.04, 0.39]	[-0.23, 0.26]	[0.02, 0.45]	[-0.13, 0.43]	[0.09, 0.36]	[-0.10, 0.26]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.09		0.15	
95% CI	[-0.10, 0.50]		[-0.27, 0.44]		[-0.08, 0.37]	
p-value	0.1832		0.6166		0.2021	
Hedges' g	0.40		0.13		0.26	
95% CI	[-0.11, 0.92]		[-0.39, 0.65]		[-0.11, 0.63]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.0 (0.08)	0.2 (0.08)	0.1 (0.10)	0.2 (0.05)	0.1 (0.06)
95% CI	[0.14, 0.36]	[-0.11, 0.20]	[0.01, 0.31]	[-0.07, 0.32]	[0.11, 0.30]	[-0.04, 0.21]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.20		0.04		0.12	
95% CI	[0.01, 0.40]		[-0.21, 0.28]		[-0.04, 0.27]	
p-value	0.0388		0.7709		0.1375	
Hedges' g	0.61		0.06		0.31	
95% CI	[0.09, 1.13]		[-0.46, 0.57]		[-0.06, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	3.8 (0.54)	3.9 (0.72)	4.0 (0.55)	3.7 (0.37)	3.9 (0.55)	3.8 (0.56)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	4.0 (0.79)	3.9 (0.56)	4.2 (0.82)	3.7 (0.60)	4.1 (0.81)	3.8 (0.59)
EAP						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	3.9 (0.71)	4.0 (0.60)	4.3 (0.80)	3.7 (0.46)	4.1 (0.77)	3.9 (0.54)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.4.14.1.s6.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	0.0 (0.15)	0.3 (0.12)	-0.1 (0.16)	0.2 (0.08)	-0.0 (0.11)
95% CI	[-0.06, 0.34]		[0.03, 0.52]		[0.05, 0.36]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.34		0.21	
95% CI	[-0.27, 0.46]		[-0.07, 0.76]		[-0.06, 0.48]	
p-value	0.6009		0.1053		0.1246	
Hedges' g	0.16		0.31		0.24	
95% CI	[-0.41, 0.74]		[-0.25, 0.87]		[-0.16, 0.65]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.08)	0.1 (0.11)	0.3 (0.10)	0.0 (0.13)	0.2 (0.06)	0.1 (0.09)
95% CI	[-0.09, 0.22]		[0.13, 0.55]		[0.07, 0.33]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.07		0.32		0.12	
95% CI	[-0.35, 0.21]		[-0.02, 0.67]		[-0.10, 0.33]	
p-value	0.6080		0.0661		0.2827	
Hedges' g	-0.12		0.39		0.16	
95% CI	[-0.69, 0.45]		[-0.15, 0.94]		[-0.23, 0.55]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_14_1_m_phos_ttlpth_pp.sas using SAS 9.4

Table 12.5.1.1.1.s6.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8679		0.9607		0.9934	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	15/36	9/23	22/48	6/16	37/84	15/39
Mean (SD)	43.3 (37.69)	46.7 (39.56)	35.4 (32.54)	28.8 (18.79)	38.6 (34.43)	39.5 (33.21)
Visit 13/ET						
n/N1	13/36	6/23	23/48	4/16	36/84	10/39
Mean (SD)	38.1 (28.36)	46.6 (28.85)	42.2 (27.77)	35.6 (23.79)	40.7 (27.65)	42.2 (26.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-4.5 (7.28)	-3.7 (10.80)	13.1 (6.81)	-2.9 (11.83)	4.0 (5.48)	-2.4 (8.81)
95% CI	[-20.28, 11.19]	[-27.01, 19.67]	[-1.62, 27.82]	[-28.42, 22.68]	[-7.27, 15.22]	[-20.50, 15.66]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.87		15.97		6.40	
95% CI	[-29.02, 27.28]		[-13.56, 45.50]		[-14.90, 27.70]	
p-value	0.9475		0.2637		0.5428	
Hedges' g	-0.02		0.16		0.12	
95% CI	[-1.02, 0.98]		[-0.91, 1.23]		[-0.63, 0.87]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_5_1_1_1_m_fgf23_ttlpth_pp.sas using SAS 9.4

Table 12.5.1.1.1.s6.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	32/42	13/22	21/37	15/23	53/79	28/45
Mean (SD)	35.9 (19.37)	31.7 (34.34)	35.3 (23.85)	26.7 (18.36)	35.6 (21.04)	29.0 (26.56)
Visit 13/ET						
n/N2	27/42	7/22	24/37	9/23	51/79	16/45
Mean (SD)	40.3 (36.53)	40.3 (42.87)	69.6 (81.18)	69.4 (50.06)	54.1 (62.81)	56.7 (47.89)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	7.4 (7.97)	1.3 (15.86)	47.5 (21.18)	41.7 (35.85)	27.3 (10.15)	21.8 (18.34)
95% CI	[-8.97, 23.81]	[-31.33, 33.86]	[3.36, 91.71]	[-33.04, 116.53]	[6.86, 47.70]	[-15.10, 58.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	6.15		5.79		5.48	
95% CI	[-30.64, 42.95]		[-81.46, 93.05]		[-36.72, 47.67]	
p-value	0.7338		0.8913		0.7951	
Hedges' g	0.34		0.01		0.07	
95% CI	[-0.54, 1.22]		[-0.89, 0.91]		[-0.57, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_5_1_1_1_m_fgf23_ttlpth_pp.sas using SAS 9.4

Table 12.5.1.1.1.s6.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	33/37	13/17	26/34	18/21	59/71	31/38
Mean (SD)	60.3 (76.14)	51.5 (33.27)	33.0 (19.70)	42.1 (31.31)	48.2 (59.61)	46.0 (31.95)
Visit 13/ET						
n/N3	29/37	9/17	20/34	12/21	49/71	21/38
Mean (SD)	60.7 (59.76)	40.9 (25.95)	73.8 (88.51)	67.9 (71.51)	66.1 (72.29)	56.3 (57.17)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	6.3 (10.80)	-14.9 (18.72)	38.9 (19.54)	27.2 (25.85)	20.4 (10.61)	8.2 (15.92)
95% CI	[-15.63, 28.33]		[-1.22, 78.97]		[-0.85, 41.59]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	21.20		11.63		12.21	
95% CI	[-22.79, 65.19]		[-55.61, 78.86]		[-26.05, 50.47]	
p-value	0.3340		0.7255		0.5258	
Hedges' g	0.17		0.17		0.11	
95% CI	[-0.57, 0.90]		[-0.56, 0.89]		[-0.41, 0.63]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_5_1_1_1_m_fgf23_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5210		0.7370		0.8225	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	36/36	23/23	48/48	16/16	84/84	39/39
Mean (SD)	37.5 (12.32)	39.3 (12.19)	33.3 (9.88)	37.3 (9.24)	35.1 (11.12)	38.5 (10.99)
Visit 13/ET						
n/N1	36/36	23/23	46/48	16/16	82/84	39/39
Mean (SD)	36.0 (12.11)	38.3 (11.87)	32.3 (12.42)	36.3 (10.48)	33.9 (12.34)	37.5 (11.22)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-1.7 (1.23)	-0.7 (1.54)	-0.3 (1.01)	-1.1 (1.74)	-1.0 (0.80)	-0.7 (1.18)
95% CI	[-4.13, 0.81]	[-3.80, 2.38]	[-2.29, 1.77]	[-4.61, 2.35]	[-2.61, 0.58]	[-3.04, 1.65]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.95		0.87		-0.32	
95% CI	[-4.91, 3.01]		[-3.19, 4.94]		[-3.16, 2.53]	
p-value	0.6318		0.6691		0.8250	
Hedges' g	-0.07		0.10		0.02	
95% CI	[-0.59, 0.45]		[-0.46, 0.66]		[-0.36, 0.40]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_2_m_egfr_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	42/42	22/22	37/37	23/23	79/79	45/45
Mean (SD)	28.6 (8.20)	30.8 (8.60)	30.4 (8.69)	33.2 (9.84)	29.5 (8.42)	32.0 (9.23)
Visit 13/ET						
n/N2	42/42	22/22	37/37	22/23	79/79	44/45
Mean (SD)	28.3 (10.09)	31.1 (10.53)	28.7 (10.24)	31.5 (11.56)	28.5 (10.10)	31.3 (10.93)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.4 (1.01)	0.3 (1.40)	-1.7 (0.97)	-1.4 (1.27)	-1.0 (0.70)	-0.5 (0.94)
95% CI	[-2.40, 1.66]	[-2.46, 3.15]	[-3.67, 0.23]	[-3.91, 1.16]	[-2.44, 0.35]	[-2.38, 1.35]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.72		-0.34		-0.53	
95% CI	[-4.19, 2.76]		[-3.56, 2.87]		[-2.87, 1.81]	
p-value	0.6821		0.8313		0.6546	
Hedges' g	-0.09		-0.05		-0.07	
95% CI	[-0.60, 0.42]		[-0.57, 0.47]		[-0.43, 0.30]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_2_m_egfr_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	37/37	17/17	34/34	21/21	71/71	38/38
Mean (SD)	25.2 (8.78)	28.5 (8.87)	27.8 (8.95)	28.0 (6.49)	26.4 (8.89)	28.2 (7.54)
Visit 13/ET						
n/N3	37/37	16/17	34/34	19/21	71/71	35/38
Mean (SD)	26.1 (11.31)	27.4 (8.82)	25.3 (9.49)	25.6 (6.98)	25.7 (10.41)	26.4 (7.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.7 (1.31)	-1.2 (2.01)	-2.4 (0.93)	-1.3 (1.24)	-0.8 (0.80)	-1.3 (1.15)
95% CI	[-1.95, 3.31]		[-4.26, -0.54]		[-2.43, 0.75]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.88		-1.06		0.47	
95% CI	[-2.97, 6.73]		[-4.17, 2.05]		[-2.31, 3.25]	
p-value	0.4394		0.4967		0.7376	
Hedges' g	0.32		-0.21		0.11	
95% CI	[-0.26, 0.90]		[-0.77, 0.34]		[-0.29, 0.51]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_12_1_2_m_egfr_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.1.s6.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5736		0.8966		0.8782	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
Baseline						
n/N1	26/36	19/23	30/48	9/16	56/84	28/39
Mean (SD)	0.8 (0.94)	0.5 (0.71)	0.6 (0.65)	0.5 (0.69)	0.7 (0.80)	0.5 (0.69)
Visit 13/ET						
n/N1	27/36	20/23	29/48	10/16	56/84	30/39
Mean (SD)	0.9 (1.33)	0.6 (1.02)	0.8 (1.14)	0.7 (0.90)	0.9 (1.23)	0.6 (0.97)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.13)	0.2 (0.15)	0.3 (0.17)	0.2 (0.30)	0.2 (0.10)	0.2 (0.15)
95% CI	[-0.14, 0.37]	[-0.10, 0.50]	[-0.03, 0.68]	[-0.39, 0.82]	[0.01, 0.43]	[-0.10, 0.51]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.09		0.11		0.02	
95% CI	[-0.49, 0.31]		[-0.59, 0.81]		[-0.35, 0.39]	
p-value	0.6615		0.7536		0.9310	
Hedges' g	-0.02		0.12		0.08	
95% CI	[-0.59, 0.55]		[-0.62, 0.87]		[-0.37, 0.52]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_15_1_1_m_ua_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.1.s6.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
Baseline						
n/N2	33/42	19/22	31/37	18/23	64/79	37/45
Mean (SD)	0.5 (0.66)	0.9 (1.32)	0.8 (1.08)	0.4 (0.76)	0.7 (0.89)	0.7 (1.10)
Visit 13/ET						
n/N2	36/42	20/22	31/37	15/23	67/79	35/45
Mean (SD)	0.5 (0.76)	0.7 (0.88)	0.9 (1.10)	0.5 (0.81)	0.7 (0.95)	0.6 (0.84)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.09)	-0.1 (0.12)	0.1 (0.13)	-0.1 (0.19)	0.1 (0.08)	-0.1 (0.11)
95% CI	[-0.20, 0.17]	[-0.35, 0.15]	[-0.15, 0.39]	[-0.44, 0.33]	[-0.10, 0.21]	[-0.30, 0.14]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.08		0.17		0.14	
95% CI	[-0.24, 0.40]		[-0.30, 0.65]		[-0.13, 0.41]	
p-value	0.6129		0.4652		0.3109	
Hedges' g	0.33		0.10		0.22	
95% CI	[-0.21, 0.88]		[-0.51, 0.71]		[-0.18, 0.63]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_15_1_1_m_ua_ttlpth_pp.sas using SAS 9.4

Table 12.4.15.1.1.s6.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
Baseline						
n/N3	34/37	15/17	28/34	19/21	62/71	34/38
Mean (SD)	0.6 (0.78)	0.6 (0.59)	0.8 (1.10)	1.3 (1.59)	0.7 (0.93)	1.0 (1.28)
Visit 13/ET						
n/N3	30/37	14/17	26/34	14/21	56/71	28/38
Mean (SD)	0.7 (0.98)	0.6 (0.73)	0.7 (0.91)	0.7 (0.57)	0.7 (0.94)	0.6 (0.64)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.12)	0.1 (0.18)	-0.1 (0.08)	-0.2 (0.11)	-0.0 (0.08)	-0.1 (0.11)
95% CI	[-0.20, 0.30]		[-0.28, 0.04]		[-0.18, 0.12]	
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.11		0.06	
95% CI	[-0.47, 0.42]		[-0.16, 0.38]		[-0.21, 0.32]	
p-value	0.9153		0.4201		0.6756	
Hedges' g	-0.06		0.30		0.11	
95% CI	[-0.68, 0.56]		[-0.34, 0.94]		[-0.34, 0.56]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_15_1_1_m_ua_ttlpth_pp.sas using SAS 9.4

Table 12.4.12.1.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5695		0.3878		0.2599	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	9.3 (0.33)	9.4 (0.36)	9.4 (0.36)	9.6 (0.19)	9.4 (0.35)	9.5 (0.30)
Visit 13/ET						
n/N1	13/13	5/5	26/27	3/4	39/40	8/9
Mean (SD)	9.7 (0.45)	9.5 (0.32)	9.8 (0.31)	9.6 (0.35)	9.8 (0.36)	9.5 (0.32)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.10)	0.1 (0.16)	0.4 (0.05)	0.1 (0.16)	0.3 (0.05)	0.1 (0.11)
95% CI	[0.14, 0.55]	[-0.25, 0.42]	[0.25, 0.47]	[-0.21, 0.43]	[0.24, 0.45]	[-0.13, 0.31]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.26		0.25		0.26	
95% CI	[-0.14, 0.66]		[-0.08, 0.59]		[0.01, 0.50]	
p-value	0.1864		0.1344		0.0415	
Hedges' g	0.76		1.01		0.92	
95% CI	[-0.26, 1.77]		[-0.18, 2.21]		[0.15, 1.69]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_1_m_dca_dose_pp.sas using SAS 9.4

Table 12.4.12.1.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	9.2 (0.26)	9.2 (0.26)	9.2 (0.28)	9.2 (0.26)	9.2 (0.27)	9.2 (0.26)
Visit 13/ET						
n/N2	102/102	56/57	91/92	54/56	193/194	110/113
Mean (SD)	9.4 (0.39)	9.3 (0.33)	9.5 (0.36)	9.3 (0.56)	9.4 (0.37)	9.3 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.03)	0.1 (0.04)	0.3 (0.04)	0.1 (0.05)	0.3 (0.03)	0.1 (0.03)
95% CI	[0.19, 0.32]	[0.03, 0.21]	[0.20, 0.36]	[0.01, 0.21]	[0.22, 0.32]	[0.05, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.13		0.17		0.15	
95% CI	[0.03, 0.24]		[0.04, 0.29]		[0.07, 0.23]	
p-value	0.0160		0.0091		0.0004	
Hedges' g	0.45		0.47		0.46	
95% CI	[0.12, 0.77]		[0.13, 0.81]		[0.22, 0.70]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_1_m_dca_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4147		0.6452		0.4812	
Comparison Baseline vs. EAP	0.2014		0.7862		0.2994	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	3.4 (0.58)	3.2 (0.50)	3.8 (0.36)	3.5 (0.39)	3.7 (0.46)	3.3 (0.45)
Visit 13/ET						
n/N1	13/13	5/5	26/27	3/4	39/40	8/9
Mean (SD)	3.8 (0.58)	3.7 (0.76)	3.9 (0.59)	3.3 (0.66)	3.9 (0.58)	3.5 (0.70)
EAP						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	3.6 (0.56)	3.6 (0.40)	3.9 (0.48)	3.5 (0.47)	3.8 (0.53)	3.6 (0.41)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.4 (0.16)	0.4 (0.26)	0.2 (0.10)	-0.2 (0.32)	0.2 (0.09)	0.1 (0.21)
95% CI	[0.01, 0.70]	[-0.17, 0.95]	[-0.04, 0.39]	[-0.87, 0.43]	[0.06, 0.44]	[-0.36, 0.47]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.03		0.40		0.19	
95% CI	[-0.69, 0.64]		[-0.30, 1.09]		[-0.26, 0.65]	
p-value	0.9257		0.2502		0.3982	
Hedges' g	-0.22		0.57		-0.04	
95% CI	[-1.21, 0.76]		[-0.60, 1.74]		[-0.79, 0.71]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.11)	0.4 (0.18)	0.2 (0.07)	0.0 (0.17)	0.2 (0.06)	0.2 (0.13)
95% CI	[-0.04, 0.43]	[-0.02, 0.74]	[0.05, 0.31]	[-0.33, 0.38]	[0.05, 0.30]	[-0.08, 0.43]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.17		0.16		0.00	
95% CI	[-0.62, 0.28]		[-0.23, 0.54]		[-0.28, 0.28]	
p-value	0.4407		0.4080		0.9945	
Hedges' g	-0.56		0.42		-0.20	
95% CI	[-1.56, 0.44]		[-0.61, 1.45]		[-0.91, 0.52]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	3.8 (0.53)	3.9 (0.57)	3.8 (0.62)	3.6 (0.45)	3.8 (0.57)	3.7 (0.52)
Visit 13/ET						
n/N2	102/102	56/57	91/92	54/56	193/194	110/113
Mean (SD)	3.9 (0.72)	3.9 (0.64)	4.1 (0.76)	3.7 (0.73)	4.0 (0.74)	3.8 (0.69)
EAP						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	3.9 (0.62)	3.9 (0.58)	4.0 (0.71)	3.8 (0.54)	4.0 (0.67)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.4.14.1.s7.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.06)	0.0 (0.08)	0.3 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.26]	[-0.11, 0.20]	[0.15, 0.41]	[-0.11, 0.23]	[0.13, 0.30]	[-0.06, 0.17]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.22		0.16	
95% CI	[-0.09, 0.29]		[0.00, 0.43]		[0.02, 0.30]	
p-value	0.2907		0.0471		0.0266	
Hedges' g	0.21		0.28		0.24	
95% CI	[-0.12, 0.53]		[-0.06, 0.62]		[0.01, 0.48]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.04)	0.1 (0.05)	0.3 (0.05)	0.1 (0.07)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.06, 0.22]	[-0.00, 0.21]	[0.17, 0.37]	[-0.04, 0.23]	[0.14, 0.27]	[0.02, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.04		0.18		0.10	
95% CI	[-0.10, 0.17]		[0.01, 0.34]		[-0.00, 0.21]	
p-value	0.5925		0.0402		0.0582	
Hedges' g	0.13		0.27		0.20	
95% CI	[-0.20, 0.45]		[-0.06, 0.60]		[-0.03, 0.43]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_14_1_m_phos_dose_pp.sas using SAS 9.4

Table 12.5.1.1.1.s7.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	NA		NA		NA	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	8/13	2/5	13/27	2/4	21/40	4/9
Mean (SD)	37.6 (24.23)	82.8 (85.91)	39.4 (30.64)	21.1 (8.91)	38.7 (27.74)	51.9 (61.27)
Visit 13/ET						
n/N1	7/13	1/5	10/27	0/4	17/40	1/9
Mean (SD)	27.6 (13.83)	18.2 (NA)	58.2 (81.85)	NA (NA)	45.6 (63.89)	18.2 (NA)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-9.2 (5.73)	-19.5 (15.52)	21.6 (32.53)	NA (NA)	5.6 (17.27)	NA (NA)
95% CI	[-23.97, 5.48]	[-59.37, 20.40]	[-58.03, 101.15]	NA	[-32.01, 43.26]	NA
Diff in LS-Mean [ER-Calcifediol - Placebo]	10.24		NA		NA	
95% CI	[-32.56, 53.04]		NA		NA	
p-value	0.5654		NA		NA	
Hedges' g	NA		NA		NA	
95% CI	NA		NA		NA	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_5_1_1_1_m_fgf23_dose_pp.sas using SAS 9.4

Table 12.5.1.1.1.s7.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	72/102	33/57	56/92	37/56	128/194	70/113
Mean (SD)	48.4 (55.93)	40.5 (31.58)	33.3 (24.03)	34.8 (26.28)	41.8 (45.33)	37.5 (28.83)
Visit 13/ET						
n/N2	62/102	21/57	57/92	25/56	119/194	46/113
Mean (SD)	50.8 (49.16)	43.4 (31.72)	62.0 (69.45)	63.3 (58.33)	56.2 (59.75)	54.2 (48.59)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	6.1 (6.40)	-5.3 (10.79)	36.5 (11.74)	29.0 (16.22)	20.8 (6.33)	11.5 (9.61)
95% CI	[-6.61, 18.91]	[-26.80, 16.24]	[13.03, 60.04]	[-3.49, 61.45]	[8.25, 33.30]	[-7.49, 30.52]
Diff in LS-Mean [ER-Calcifediol - Placebo]	11.43		7.56		9.26	
95% CI	[-13.59, 36.45]		[-32.58, 47.70]		[-13.51, 32.04]	
p-value	0.3655		0.7075		0.4224	
Hedges' g	0.21		0.14		0.13	
95% CI	[-0.31, 0.73]		[-0.38, 0.66]		[-0.24, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_5_1_1_1_m_fgf23_dose_pp.sas using SAS 9.4

Table 12.4.12.1.2.s7.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1465		0.3945		0.6880	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	13/13	5/5	27/27	4/4	40/40	9/9
Mean (SD)	29.1 (8.51)	42.6 (13.48)	32.8 (9.60)	42.3 (8.54)	31.6 (9.32)	42.4 (10.88)
Visit 13/ET						
n/N1	13/13	5/5	26/27	3/4	39/40	8/9
Mean (SD)	29.0 (11.78)	37.8 (16.08)	32.2 (14.02)	45.7 (10.97)	31.1 (13.25)	40.8 (14.10)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.6 (1.63)	-6.6 (2.84)	-0.1 (1.59)	2.9 (4.84)	0.3 (1.25)	-1.8 (2.80)
95% CI	[-2.86, 4.08]	[-12.63, -0.55]	[-3.38, 3.17]	[-7.04, 12.87]	[-2.26, 2.78]	[-7.47, 3.84]
Diff in LS-Mean [ER-Calcifediol - Placebo]	7.20		-3.02		2.08	
95% CI	[-0.22, 14.62]		[-13.58, 7.54]		[-4.29, 8.44]	
p-value	0.0562		0.5614		0.5138	
Hedges' g	0.79		-0.55		0.16	
95% CI	[-0.22, 1.81]		[-1.72, 0.62]		[-0.59, 0.90]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_2_m_egfr_dose_pp.sas using SAS 9.4

Table 12.4.12.1.2.s7.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	102/102	57/57	92/92	56/56	194/194	113/113
Mean (SD)	30.5 (11.29)	32.5 (10.56)	30.2 (9.39)	31.8 (8.96)	30.3 (10.41)	32.2 (9.77)
Visit 13/ET						
n/N2	102/102	56/57	91/92	54/56	193/194	110/113
Mean (SD)	30.1 (11.86)	32.4 (11.01)	28.3 (10.23)	30.1 (10.10)	29.3 (11.13)	31.3 (10.59)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.5 (0.72)	-0.1 (0.98)	-1.7 (0.58)	-1.5 (0.76)	-1.1 (0.47)	-0.8 (0.63)
95% CI	[-1.91, 0.95]	[-2.00, 1.87]	[-2.87, -0.57]	[-2.99, 0.00]	[-2.04, -0.18]	[-2.01, 0.45]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.42		-0.23		-0.33	
95% CI	[-2.83, 1.99]		[-2.12, 1.66]		[-1.87, 1.22]	
p-value	0.7339		0.8119		0.6750	
Hedges' g	0.00		-0.02		-0.00	
95% CI	[-0.32, 0.33]		[-0.36, 0.31]		[-0.24, 0.23]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn’t meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_12_1_2_m_egfr_dose_pp.sas using SAS 9.4

Table 12.4.15.1.1.s7.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.3375		NA		0.8571	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
Baseline						
n/N1	11/13	5/5	19/27	1/4	30/40	6/9
Mean (SD)	0.8 (0.99)	0.1 (0.07)	0.5 (0.69)	5.7 (NA)	0.6 (0.80)	1.0 (2.30)
Visit 13/ET						
n/N1	10/13	5/5	16/27	1/4	26/40	6/9
Mean (SD)	0.6 (0.66)	0.1 (0.16)	0.8 (1.11)	0.4 (NA)	0.7 (0.96)	0.2 (0.18)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.1 (0.14)	-0.2 (0.20)	0.2 (0.25)	-0.2 (0.99)	0.0 (0.16)	-0.2 (0.43)
95% CI	[-0.40, 0.21]	[-0.67, 0.21]	[-0.31, 0.76]	[-2.33, 1.93]	[-0.28, 0.37]	[-1.07, 0.70]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.14		0.42		0.23	
95% CI	[-0.41, 0.69]		[-1.77, 2.62]		[-0.72, 1.18]	
p-value	0.5904		0.6857		0.6202	
Hedges' g	-0.39		NA		0.07	
95% CI	[-1.41, 0.63]		NA		[-0.80, 0.93]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_15_1_1_m_ua_dose_pp.sas using SAS 9.4

Table 12.4.15.1.1.s7.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
Baseline						
n/N2	82/102	48/57	70/92	45/56	152/194	93/113
Mean (SD)	0.6 (0.76)	0.7 (0.98)	0.8 (1.02)	0.7 (0.99)	0.7 (0.89)	0.7 (0.98)
Visit 13/ET						
n/N2	83/102	49/57	70/92	38/56	153/194	87/113
Mean (SD)	0.7 (1.06)	0.7 (0.91)	0.8 (1.05)	0.6 (0.75)	0.8 (1.05)	0.7 (0.84)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.0 (0.10)	0.1 (0.08)	-0.1 (0.11)	0.1 (0.06)	-0.0 (0.07)
95% CI	[-0.04, 0.25]	[-0.17, 0.20]	[-0.08, 0.25]	[-0.28, 0.16]	[-0.02, 0.20]	[-0.16, 0.13]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.09		0.14		0.11	
95% CI	[-0.15, 0.33]		[-0.13, 0.41]		[-0.07, 0.29]	
p-value	0.4656		0.2969		0.2428	
Hedges' g	0.14		0.16		0.15	
95% CI	[-0.21, 0.49]		[-0.24, 0.56]		[-0.12, 0.41]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_15_1_1_m_ua_dose_pp.sas using SAS 9.4

Table 12.4.12.1.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1212		0.0297		0.7169	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	9.2 (0.27)	9.2 (0.23)	9.3 (0.32)	9.1 (0.27)	9.2 (0.30)	9.2 (0.24)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	9.3 (0.45)	9.3 (0.34)	9.7 (0.43)	9.1 (0.47)	9.5 (0.48)	9.2 (0.40)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	0.1 (0.12)	0.5 (0.07)	-0.0 (0.12)	0.3 (0.06)	0.1 (0.08)
95% CI	[-0.10, 0.32]	[-0.12, 0.39]	[0.31, 0.62]	[-0.25, 0.23]	[0.17, 0.41]	[-0.12, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.02		0.48		0.24	
95% CI	[-0.35, 0.30]		[0.19, 0.76]		[0.02, 0.45]	
p-value	0.8777		0.0023		0.0300	
Hedges' g	-0.08		1.46		0.61	
95% CI	[-0.85, 0.70]		[0.57, 2.35]		[0.04, 1.19]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_1_m_dca_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	9.2 (0.28)	9.3 (0.28)	9.2 (0.32)	9.3 (0.27)	9.2 (0.30)	9.3 (0.28)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	9.5 (0.39)	9.3 (0.33)	9.5 (0.36)	9.4 (0.55)	9.5 (0.37)	9.4 (0.45)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.03)	0.1 (0.05)	0.3 (0.04)	0.1 (0.05)	0.3 (0.02)	0.1 (0.03)
95% CI	[0.22, 0.35]	[0.02, 0.20]	[0.20, 0.34]	[0.03, 0.23]	[0.23, 0.33]	[0.05, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.14		0.16	
95% CI	[0.07, 0.29]		[0.01, 0.26]		[0.08, 0.24]	
p-value	0.0018		0.0303		0.0002	
Hedges' g	0.59		0.40		0.50	
95% CI	[0.25, 0.93]		[0.06, 0.75]		[0.25, 0.74]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_1_m_dca_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1984		0.8259		0.4794	
Comparison Baseline vs. EAP	0.7725		0.7347		0.8110	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	3.6 (0.40)	3.9 (0.50)	3.8 (0.54)	4.0 (0.45)	3.7 (0.49)	4.0 (0.47)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	3.8 (0.45)	3.8 (0.64)	4.1 (1.03)	4.2 (0.64)	4.0 (0.83)	3.9 (0.65)
EAP						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	3.7 (0.40)	4.0 (0.38)	4.1 (0.84)	4.2 (0.46)	3.9 (0.71)	4.1 (0.42)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.13)	-0.1 (0.16)	0.3 (0.19)	0.2 (0.30)	0.2 (0.12)	0.0 (0.17)
95% CI	[-0.15, 0.38]	[-0.42, 0.24]	[-0.06, 0.74]	[-0.41, 0.83]	[-0.01, 0.48]	[-0.29, 0.38]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.21		0.13		0.19	
95% CI	[-0.23, 0.64]		[-0.61, 0.88]		[-0.23, 0.61]	
p-value	0.3395		0.7128		0.3737	
Hedges' g	0.66		0.19		0.41	
95% CI	[-0.14, 1.45]		[-0.61, 0.99]		[-0.16, 0.98]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	-0.0 (0.09)	0.2 (0.11)	0.3 (0.14)	0.3 (0.22)	0.2 (0.09)	0.2 (0.12)
95% CI	[-0.20, 0.17]	[-0.06, 0.40]	[0.05, 0.63]	[-0.17, 0.73]	[-0.00, 0.35]	[-0.03, 0.46]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.18		0.06		-0.04	
95% CI	[-0.49, 0.12]		[-0.48, 0.60]		[-0.35, 0.27]	
p-value	0.2263		0.8196		0.8013	
Hedges' g	-0.04		0.13		0.11	
95% CI	[-0.82, 0.73]		[-0.67, 0.93]		[-0.45, 0.67]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	3.7 (0.56)	3.8 (0.61)	3.8 (0.58)	3.6 (0.42)	3.8 (0.57)	3.7 (0.53)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	3.9 (0.74)	3.9 (0.66)	4.0 (0.66)	3.6 (0.72)	4.0 (0.70)	3.8 (0.69)
EAP						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	3.9 (0.64)	3.9 (0.60)	4.0 (0.63)	3.7 (0.51)	4.0 (0.64)	3.8 (0.57)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.4.14.1.s8.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.08)	0.2 (0.06)	0.0 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.06, 0.29]	[-0.04, 0.28]	[0.13, 0.35]	[-0.14, 0.18]	[0.13, 0.29]	[-0.04, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.05		0.22		0.14	
95% CI	[-0.15, 0.25]		[0.03, 0.42]		[-0.00, 0.28]	
p-value	0.6181		0.0254		0.0517	
Hedges' g	0.09		0.29		0.19	
95% CI	[-0.24, 0.43]		[-0.05, 0.63]		[-0.05, 0.43]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.04)	0.1 (0.06)	0.2 (0.04)	0.1 (0.06)	0.2 (0.03)	0.1 (0.04)
95% CI	[0.08, 0.25]	[0.02, 0.25]	[0.15, 0.33]	[-0.07, 0.18]	[0.14, 0.26]	[0.02, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		0.18		0.10	
95% CI	[-0.11, 0.17]		[0.03, 0.34]		[-0.00, 0.20]	
p-value	0.6971		0.0188		0.0555	
Hedges' g	0.08		0.28		0.19	
95% CI	[-0.25, 0.41]		[-0.05, 0.62]		[-0.05, 0.42]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_14_1_m_phos_vitd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s8.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4523		0.5276		0.4584	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	11/15	5/10	11/19	3/8	22/34	8/18
Mean (SD)	59.2 (44.32)	43.0 (42.80)	29.8 (25.13)	48.1 (37.78)	44.5 (38.24)	44.9 (38.23)
Visit 13/ET						
n/N1	8/15	2/10	12/19	3/8	20/34	5/18
Mean (SD)	59.6 (28.39)	61.6 (34.29)	75.8 (113.15)	67.2 (44.27)	69.3 (88.18)	65.0 (35.83)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.6 (13.08)	7.6 (26.20)	75.8 (50.36)	22.9 (78.03)	43.0 (26.17)	12.7 (46.73)
95% CI	[-23.36, 40.65]	[-56.54, 71.70]	[-43.27, 194.89]	[-161.57, 207.44]	[-13.09, 99.18]	[-87.53, 112.91]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.06		52.88		30.36	
95% CI	[-73.48, 75.61]		[-169.95, 275.71]		[-87.50, 148.23]	
p-value	0.9733		0.5922		0.5893	
Hedges' g	0.72		0.43		0.44	
95% CI	[-0.72, 2.16]		[-0.81, 1.66]		[-0.55, 1.42]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_5_1_1_1_m_fgf23_vitd_pp.sas using SAS 9.4

Table 12.5.1.1.1.s8.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	69/100	30/52	58/100	36/52	127/200	66/104
Mean (SD)	45.4 (54.98)	42.9 (34.91)	35.3 (25.41)	32.9 (24.96)	40.8 (44.15)	37.5 (30.07)
Visit 13/ET						
n/N2	61/100	20/52	55/100	22/52	116/200	42/104
Mean (SD)	47.0 (49.19)	40.4 (31.40)	58.3 (58.80)	62.7 (60.82)	52.4 (54.02)	52.1 (49.79)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	3.5 (6.40)	-6.6 (11.09)	27.8 (10.15)	28.0 (15.32)	15.3 (5.77)	10.3 (9.28)
95% CI	[-9.24, 16.30]	[-28.72, 15.51]	[7.46, 48.14]	[-2.74, 58.66]	[3.88, 26.70]	[-8.09, 28.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	10.13		-0.16		5.02	
95% CI	[-15.40, 35.67]		[-36.99, 36.66]		[-16.60, 26.64]	
p-value	0.4313		0.9930		0.6469	
Hedges' g	0.13		-0.01		0.04	
95% CI	[-0.39, 0.66]		[-0.56, 0.54]		[-0.34, 0.42]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_5_1_1_1_m_fgf23_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.0993		0.9596		0.3536	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	26.3 (8.03)	34.3 (13.65)	31.5 (9.75)	25.8 (6.23)	29.2 (9.27)	30.5 (11.56)
Visit 13/ET						
n/N1	15/15	10/10	19/19	8/8	34/34	18/18
Mean (SD)	29.1 (11.54)	32.8 (12.00)	28.9 (13.27)	23.4 (7.69)	29.0 (12.36)	28.6 (11.13)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	2.7 (1.61)	-1.3 (2.00)	-2.9 (1.31)	-1.6 (2.06)	0.2 (1.02)	-2.0 (1.40)
95% CI	[-0.69, 6.00]	[-5.44, 2.87]	[-5.62, -0.19]	[-5.86, 2.66]	[-1.90, 2.21]	[-4.78, 0.86]
Diff in LS-Mean [ER-Calcifediol - Placebo]	3.94		-1.31		2.11	
95% CI	[-1.56, 9.44]		[-6.45, 3.84]		[-1.38, 5.61]	
p-value	0.1517		0.6051		0.2295	
Hedges' g	0.70		-0.03		0.27	
95% CI	[-0.10, 1.50]		[-0.84, 0.77]		[-0.30, 0.83]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_2_m_egfr_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.2.s6.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	100/100	52/52	100/100	52/52	200/200	104/104
Mean (SD)	30.9 (11.28)	33.1 (10.63)	30.7 (9.45)	33.5 (9.24)	30.8 (10.38)	33.3 (9.91)
Visit 13/ET						
n/N2	100/100	51/52	98/100	49/52	198/200	100/104
Mean (SD)	30.1 (11.89)	32.9 (11.44)	29.2 (10.88)	32.1 (10.61)	29.7 (11.38)	32.5 (10.99)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.9 (0.74)	-0.3 (1.03)	-1.2 (0.62)	-1.0 (0.88)	-1.1 (0.48)	-0.6 (0.68)
95% CI	[-2.37, 0.54]	[-2.31, 1.77]	[-2.40, 0.06]	[-2.73, 0.76]	[-2.01, -0.10]	[-1.94, 0.75]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.65		-0.18		-0.46	
95% CI	[-3.16, 1.87]		[-2.33, 1.96]		[-2.11, 1.20]	
p-value	0.6131		0.8667		0.5873	
Hedges' g	-0.03		-0.01		-0.02	
95% CI	[-0.36, 0.31]		[-0.35, 0.33]		[-0.26, 0.22]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_12_1_2_m_egfr_vitd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s8.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.6552		0.2158		0.1931	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
Baseline						
n/N1	13/15	8/10	13/19	7/8	26/34	15/18
Mean (SD)	0.8 (1.00)	0.5 (0.93)	1.0 (1.28)	0.7 (0.77)	0.9 (1.14)	0.6 (0.84)
Visit 13/ET						
n/N1	10/15	7/10	12/19	5/8	22/34	12/18
Mean (SD)	0.8 (0.71)	0.2 (0.37)	1.3 (1.44)	0.6 (0.78)	1.1 (1.17)	0.4 (0.57)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.0 (0.14)	-0.5 (0.17)	0.2 (0.22)	-0.4 (0.34)	0.1 (0.14)	-0.4 (0.19)
95% CI	[-0.34, 0.26]	[-0.81, -0.10]	[-0.23, 0.70]	[-1.11, 0.32]	[-0.21, 0.37]	[-0.80, -0.01]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.41		0.63		0.48	
95% CI	[-0.06, 0.88]		[-0.23, 1.48]		[-0.01, 0.98]	
p-value	0.0805		0.1377		0.0549	
Hedges' g	0.27		0.80		0.57	
95% CI	[-0.65, 1.19]		[-0.23, 1.82]		[-0.13, 1.27]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_15_1_1_m_ua_vitd_pp.sas using SAS 9.4

Table 12.4.15.1.1.s8.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
Baseline						
n/N2	80/100	45/52	76/100	39/52	156/200	84/104
Mean (SD)	0.6 (0.75)	0.7 (0.97)	0.7 (0.89)	0.8 (1.30)	0.6 (0.82)	0.8 (1.13)
Visit 13/ET						
n/N2	83/100	47/52	74/100	34/52	157/200	81/104
Mean (SD)	0.7 (1.06)	0.7 (0.92)	0.7 (0.97)	0.6 (0.75)	0.7 (1.02)	0.7 (0.85)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.07)	0.1 (0.09)	0.1 (0.08)	-0.0 (0.12)	0.1 (0.06)	0.0 (0.08)
95% CI	[-0.05, 0.23]	[-0.12, 0.25]	[-0.08, 0.25]	[-0.25, 0.23]	[-0.02, 0.20]	[-0.12, 0.19]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.03		0.09		0.05	
95% CI	[-0.21, 0.26]		[-0.20, 0.39]		[-0.13, 0.24]	
p-value	0.8257		0.5219		0.5759	
Hedges' g	0.04		0.10		0.07	
95% CI	[-0.31, 0.40]		[-0.31, 0.51]		[-0.20, 0.34]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_15_1_1_m_ua_vitd_pp.sas using SAS 9.4

Table 12.4.12.1.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.4920		0.3086		0.8023	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	9.2 (0.28)	9.2 (0.28)	9.2 (0.29)	9.3 (0.21)	9.2 (0.29)	9.3 (0.25)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	9.5 (0.40)	9.3 (0.34)	9.5 (0.39)	9.4 (0.61)	9.5 (0.39)	9.3 (0.48)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.1 (0.06)	0.2 (0.05)	0.1 (0.07)	0.3 (0.03)	0.1 (0.05)
95% CI	[0.17, 0.35]	[-0.04, 0.19]	[0.15, 0.35]	[-0.05, 0.25]	[0.19, 0.32]	[-0.00, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.18		0.15		0.16	
95% CI	[0.04, 0.33]		[-0.03, 0.33]		[0.05, 0.28]	
p-value	0.0132		0.1044		0.0057	
Hedges' g	0.58		0.38		0.49	
95% CI	[0.15, 1.00]		[-0.07, 0.84]		[0.17, 0.80]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_1_m_dca_bl25d_pp.sas using SAS 9.4

Table 12.4.12.1.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Calcium Corrected (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	9.2 (0.27)	9.2 (0.27)	9.3 (0.34)	9.2 (0.32)	9.2 (0.31)	9.2 (0.29)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	9.5 (0.40)	9.4 (0.31)	9.6 (0.35)	9.3 (0.49)	9.5 (0.38)	9.4 (0.41)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.3 (0.04)	0.2 (0.06)	0.4 (0.04)	0.1 (0.06)	0.3 (0.03)	0.1 (0.04)
95% CI	[0.18, 0.36]	[0.04, 0.29]	[0.28, 0.45]	[-0.02, 0.22]	[0.26, 0.38]	[0.04, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.11		0.26		0.19	
95% CI	[-0.05, 0.26]		[0.12, 0.41]		[0.08, 0.29]	
p-value	0.1768		0.0006		0.0006	
Hedges' g	0.36		0.72		0.54	
95% CI	[-0.10, 0.81]		[0.27, 1.16]		[0.22, 0.86]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_1_m_dca_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.8111		0.6301		0.8718	
Comparison Baseline vs. EAP	0.6859		0.5962		0.8725	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	3.8 (0.50)	3.7 (0.58)	3.8 (0.62)	3.6 (0.41)	3.8 (0.56)	3.7 (0.51)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	3.9 (0.68)	3.7 (0.60)	4.1 (0.86)	3.8 (0.76)	4.0 (0.78)	3.8 (0.67)
EAP						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	3.9 (0.53)	3.8 (0.57)	4.1 (0.78)	3.8 (0.55)	4.0 (0.67)	3.8 (0.55)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.08)	0.0 (0.10)	0.3 (0.08)	0.2 (0.12)	0.2 (0.06)	0.1 (0.08)
95% CI	[0.03, 0.33]	[-0.19, 0.21]	[0.14, 0.47]	[-0.06, 0.42]	[0.13, 0.36]	[-0.06, 0.25]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.17		0.13		0.15	
95% CI	[-0.08, 0.42]		[-0.17, 0.42]		[-0.04, 0.35]	
p-value	0.1765		0.4005		0.1226	
Hedges' g	0.21		0.19		0.21	
95% CI	[-0.21, 0.63]		[-0.26, 0.64]		[-0.10, 0.52]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.1 (0.05)	0.1 (0.07)	0.3 (0.07)	0.1 (0.09)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.24]	[-0.01, 0.25]	[0.16, 0.43]	[-0.09, 0.29]	[0.14, 0.30]	[-0.00, 0.22]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.19		0.11	
95% CI	[-0.14, 0.19]		[-0.03, 0.42]		[-0.03, 0.25]	
p-value	0.7812		0.0952		0.1126	
Hedges' g	0.01		0.34		0.19	
95% CI	[-0.41, 0.42]		[-0.10, 0.78]		[-0.11, 0.49]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	3.7 (0.58)	3.9 (0.59)	3.8 (0.53)	3.6 (0.47)	3.7 (0.55)	3.8 (0.55)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	3.9 (0.74)	4.0 (0.67)	3.9 (0.56)	3.6 (0.68)	3.9 (0.65)	3.8 (0.71)
EAP						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	3.8 (0.70)	4.0 (0.57)	4.0 (0.54)	3.7 (0.53)	3.9 (0.63)	3.9 (0.56)

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.4.14.1.s9.pp
Summary of Laboratory Concentration Change from Baseline for Serum Phosphorous (mg/dL)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (0.07)	0.1 (0.11)	0.2 (0.07)	-0.1 (0.10)	0.2 (0.05)	0.1 (0.07)
95% CI	[0.01, 0.31]	[-0.07, 0.36]	[0.07, 0.35]	[-0.27, 0.13]	[0.07, 0.28]	[-0.09, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.01		0.28		0.12	
95% CI	[-0.25, 0.28]		[0.03, 0.53]		[-0.06, 0.30]	
p-value	0.9122		0.0259		0.1873	
Hedges' g	0.13		0.34		0.25	
95% CI	[-0.32, 0.58]		[-0.09, 0.78]		[-0.07, 0.56]	
Comparison Baseline vs. EAP						
LS-Mean change from baseline (SEM)	0.2 (0.06)	0.1 (0.09)	0.2 (0.06)	0.1 (0.08)	0.2 (0.04)	0.1 (0.06)
95% CI	[0.04, 0.27]	[-0.04, 0.30]	[0.10, 0.32]	[-0.08, 0.23]	[0.09, 0.25]	[0.01, 0.23]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.02		0.13		0.05	
95% CI	[-0.19, 0.23]		[-0.06, 0.32]		[-0.08, 0.19]	
p-value	0.8431		0.1839		0.4409	
Hedges' g	0.13		0.17		0.16	
95% CI	[-0.32, 0.59]		[-0.26, 0.61]		[-0.16, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; EAP: Efficacy Assessment Phase; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_14_1_m_phos_bl25d_pp.sas using SAS 9.4

Table 12.5.1.1.1.s9.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5049		0.8096		0.9927	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	39/58	20/35	35/59	21/30	74/117	41/65
Mean (SD)	40.8 (35.51)	45.0 (34.76)	31.3 (21.11)	32.3 (24.88)	36.4 (29.78)	38.5 (30.41)
Visit 13/ET						
n/N1	36/58	13/35	36/59	16/30	72/117	29/65
Mean (SD)	35.6 (26.48)	35.4 (28.71)	62.7 (79.30)	60.9 (68.09)	49.2 (60.27)	49.5 (54.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.2 (4.94)	-4.3 (8.03)	36.9 (16.19)	32.1 (22.45)	19.4 (8.10)	11.6 (12.09)
95% CI	[-9.83, 10.13]	[-20.48, 11.97]	[4.06, 69.78]	[-13.48, 77.66]	[3.27, 35.52]	[-12.54, 35.64]
Diff in LS-Mean [ER-Calcifediol - Placebo]	4.40		4.84		7.85	
95% CI	[-14.84, 23.65]		[-51.35, 61.02]		[-21.23, 36.92]	
p-value	0.6461		0.8623		0.5925	
Hedges' g	0.42		0.06		0.11	
95% CI	[-0.24, 1.08]		[-0.60, 0.71]		[-0.36, 0.58]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_5_1_1_1_m_fgf23_bl25d_pp.sas using SAS 9.4

Table 12.5.1.1.1.s9.pp
Summary of Observed Laboratory Concentration Change from Baseline for Fibroblast Growth Factor 23 (ng/L)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	41/57	15/27	34/60	18/30	75/117	33/57
Mean (SD)	53.5 (66.32)	40.1 (37.32)	37.6 (28.90)	36.2 (27.40)	46.3 (53.04)	38.0 (31.82)
Visit 13/ET						
n/N2	33/57	9/27	31/60	9/30	64/117	18/57
Mean (SD)	62.4 (59.94)	52.3 (34.13)	60.0 (60.64)	67.4 (38.49)	61.2 (59.81)	59.9 (36.14)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	8.2 (10.76)	-6.4 (20.84)	30.7 (12.54)	24.7 (21.30)	19.0 (8.30)	7.2 (14.97)
95% CI	[-13.68, 29.99]	[-48.67, 35.96]	[4.97, 56.34]	[-18.95, 68.29]	[2.40, 35.54]	[-22.74, 37.06]
Diff in LS-Mean [ER-Calcifediol - Placebo]	14.51		5.98		11.81	
95% CI	[-33.13, 62.14]		[-44.70, 56.67]		[-22.37, 45.99]	
p-value	0.5404		0.8107		0.4926	
Hedges' g	0.08		0.18		0.11	
95% CI	[-0.69, 0.84]		[-0.60, 0.97]		[-0.45, 0.66]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.11.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_5_1_1_1_m_fgf23_bl25d_pp.sas using SAS 9.4

Table 12.4.12.1.2.s9.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.1035		0.6871		0.1454	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	58/58	35/35	59/59	30/30	117/117	65/65
Mean (SD)	29.9 (11.56)	33.7 (11.94)	30.4 (9.88)	31.2 (8.51)	30.2 (10.70)	32.5 (10.49)
Visit 13/ET						
n/N1	58/58	34/35	58/59	27/30	116/117	61/65
Mean (SD)	30.0 (12.51)	32.1 (11.63)	28.3 (11.00)	28.2 (9.35)	29.2 (11.76)	30.4 (10.77)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.2 (1.07)	-1.4 (1.41)	-1.7 (0.75)	-2.0 (1.10)	-0.9 (0.66)	-1.8 (0.92)
95% CI	[-2.38, 1.89]	[-4.23, 1.37]	[-3.22, -0.23]	[-4.22, 0.16]	[-2.25, 0.36]	[-3.63, 0.00]
Diff in LS-Mean [ER-Calcifediol - Placebo]	1.19		0.31		0.87	
95% CI	[-2.36, 4.73]		[-2.34, 2.95]		[-1.37, 3.11]	
p-value	0.5074		0.8192		0.4450	
Hedges' g	0.24		0.05		0.16	
95% CI	[-0.18, 0.67]		[-0.40, 0.51]		[-0.15, 0.47]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_2_m_egfr_bl25d_pp.sas using SAS 9.4

Table 12.4.12.1.2.s9.pp
Summary of Laboratory Concentration Change from Baseline for eGFR (mL/min/1.73m²)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	57/57	27/27	60/60	30/30	117/117	57/57
Mean (SD)	30.7 (10.47)	32.9 (9.98)	31.2 (9.10)	33.8 (9.90)	30.9 (9.75)	33.4 (9.86)
Visit 13/ET						
n/N2	57/57	27/27	59/60	30/30	116/117	57/57
Mean (SD)	30.0 (11.14)	33.8 (11.31)	29.9 (11.51)	33.3 (11.30)	30.0 (11.28)	33.5 (11.21)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	-0.8 (0.79)	1.0 (1.14)	-1.0 (0.84)	-0.6 (1.19)	-0.9 (0.58)	0.3 (0.83)
95% CI	[-2.32, 0.81]	[-1.23, 3.32]	[-2.68, 0.67]	[-2.92, 1.80]	[-2.03, 0.25]	[-1.38, 1.89]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-1.80		-0.45		-1.14	
95% CI	[-4.57, 0.97]		[-3.36, 2.47]		[-3.14, 0.85]	
p-value	0.1998		0.7618		0.2600	
Hedges' g	-0.27		-0.07		-0.16	
95% CI	[-0.73, 0.18]		[-0.51, 0.36]		[-0.48, 0.15]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; eGFR: estimated Glomerular Filtration Rate; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the average of multiple screening visit measurements; EAP : Average of Visit 10,11,12 and 13; Change from baseline : EAP-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_12_1_2_m_egfr_bl25d_pp.sas using SAS 9.4

Table 12.4.15.1.1.s9.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Interaction p-value						
Comparison Baseline vs. Visit 13/ET	0.5900		0.5098		0.9105	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
Baseline						
n/N1	51/58	33/35	47/59	24/30	98/117	57/65
Mean (SD)	0.7 (0.78)	0.7 (0.97)	0.8 (1.08)	1.0 (1.45)	0.7 (0.93)	0.8 (1.20)
Visit 13/ET						
n/N1	53/58	31/35	45/59	20/30	98/117	51/65
Mean (SD)	0.7 (1.07)	0.6 (0.82)	0.9 (1.12)	0.8 (0.80)	0.8 (1.09)	0.7 (0.81)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.0 (0.10)	-0.1 (0.12)	0.1 (0.11)	0.0 (0.17)	0.1 (0.07)	-0.0 (0.10)
95% CI	[-0.14, 0.24]	[-0.30, 0.19]	[-0.15, 0.27]	[-0.32, 0.34]	[-0.09, 0.20]	[-0.23, 0.18]
Diff in LS-Mean [ER-Calcifediol - Placebo]	0.10		0.05		0.08	
95% CI	[-0.21, 0.42]		[-0.34, 0.45]		[-0.17, 0.33]	
p-value	0.5080		0.7831		0.5322	
Hedges' g	0.16		0.07		0.13	
95% CI	[-0.28, 0.60]		[-0.46, 0.60]		[-0.21, 0.46]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_15_1_1_m_ua_bl25d_pp.sas using SAS 9.4

Table 12.4.15.1.1.s9.pp
Summary of laboratory concentration Change from Baseline for Urine Albumin/Creatinine (g/g Creatinine)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
Baseline						
n/N2	42/57	20/27	42/60	22/30	84/117	42/57
Mean (SD)	0.6 (0.81)	0.6 (0.95)	0.6 (0.80)	0.6 (0.88)	0.6 (0.80)	0.6 (0.90)
Visit 13/ET						
n/N2	40/57	23/27	41/60	19/30	81/117	42/57
Mean (SD)	0.7 (0.98)	0.7 (0.98)	0.7 (0.98)	0.4 (0.64)	0.7 (0.98)	0.6 (0.85)
Comparison Baseline vs. Visit 13/ET						
LS-Mean change from baseline (SEM)	0.1 (0.10)	0.1 (0.13)	0.2 (0.11)	-0.1 (0.16)	0.1 (0.08)	-0.0 (0.10)
95% CI	[-0.10, 0.29]	[-0.15, 0.36]	[-0.06, 0.40]	[-0.44, 0.21]	[-0.02, 0.28]	[-0.21, 0.20]
Diff in LS-Mean [ER-Calcifediol - Placebo]	-0.01		0.28		0.13	
95% CI	[-0.33, 0.31]		[-0.12, 0.68]		[-0.12, 0.38]	
p-value	0.9425		0.1595		0.3029	
Hedges' g	-0.03		0.33		0.15	
95% CI	[-0.53, 0.48]		[-0.22, 0.88]		[-0.22, 0.53]	

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; Diff: Difference; ER: Extended Release; ET: End of Treatment; LS: Least Square; PP: Per-Protocol; SD: Standard Deviation; SEM: Standard Error of the Mean.
Statistical methods: The LS mean and LS mean difference of change from baseline are estimated from ANCOVA model that includes study, treatment and study-by-treatment interaction as fixed effects and baseline value as a covariate. The subgroup interaction p-value is calculated from Hedges' g using the fixed-effect model.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.8.1
Baseline: Baseline is defined as the last non-missing measurement prior to the start of study drug; Change from baseline : Visit 13-Baseline
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_15_1_1_m_ua_bl25d_pp.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalysen zu den Sicherheitsendpunkten (Unerwünschte Ereignisse (ITT-Population))

Folgende Daten werden für die ITT-Population:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (akutes Nierenversagen, Herzerkrankung
  - UE ohne erkrankungsbezogene Ereignisse

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.9089		0.6225		0.7477	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	43/59 (72.9)	24/30 (80.0)	32/50 (64.0)	21/32 (65.6)	75/109 (68.8)	45/62 (72.6)
RR [95%-CI]; p-value	0.91 [0.72, 1.15], 0.4412		0.98 [0.70, 1.35], 0.8801		0.95 [0.78, 1.16], 0.5980	
OR [95%-CI]; p-value	0.67 [0.23, 1.94], 0.4618		0.93 [0.37, 2.36], 0.8807		0.83 [0.42, 1.66], 0.6041	
RD [95%-CI]; p-value	-0.07 [-0.25, 0.11], 0.4449		-0.02 [-0.23, 0.20], 0.8804		-0.04 [-0.18, 0.10], 0.6001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	58/82 (70.7)	32/42 (76.2)	59/94 (62.8)	23/40 (57.5)	117/176 (66.5)	55/82 (67.1)
RR [95%-CI]; p-value	0.93 [0.75, 1.16], 0.5059		1.09 [0.80, 1.49], 0.5778		0.99 [0.82, 1.19], 0.9244	
OR [95%-CI]; p-value	0.76 [0.32, 1.78], 0.5190		1.25 [0.59, 2.65], 0.5670		0.97 [0.56, 1.70], 0.9247	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.11], 0.5093		0.05 [-0.13, 0.23], 0.5700		-0.01 [-0.13, 0.12], 0.9246	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.4501		0.8354		0.7728	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	7/59 (11.9)	6/30 (20.0)	9/50 (18.0)	1/32 (3.1)	16/109 (14.7)	7/62 (11.3)
RR [95%-CI]; p-value	0.59 [0.22, 1.61], 0.3051		5.76 [0.77, 43.32], 0.0890		1.30 [0.57, 2.99], 0.5362	
OR [95%-CI]; p-value	0.54 [0.16, 1.78], 0.3043		6.80 [0.82, 56.58], 0.0446		1.35 [0.52, 3.49], 0.5324	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.08], 0.3345		0.15 [0.03, 0.27], 0.0172		0.03 [-0.07, 0.14], 0.5193	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	5/42 (11.9)	10/94 (10.6)	1/40 (2.5)	20/176 (11.4)	6/82 (7.3)
RR [95%-CI]; p-value	1.02 [0.37, 2.80], 0.9626		4.26 [0.56, 32.14], 0.1604		1.55 [0.65, 3.72], 0.3235	
OR [95%-CI]; p-value	1.03 [0.33, 3.23], 0.9626		4.64 [0.57, 37.55], 0.1163		1.62 [0.63, 4.21], 0.3147	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9624		0.08 [0.00, 0.16], 0.0432		0.04 [-0.03, 0.11], 0.2794	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.2381		0.8988		0.4003	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	0/30 (0.0)	5/50 (10.0)	4/32 (12.5)	11/109 (10.1)	4/62 (6.5)
RR [95%-CI]; p-value	6.20 [0.36, 107.42], 0.2097		0.80 [0.23, 2.76], 0.7238		1.56 [0.52, 4.70], 0.4258	
OR [95%-CI]; p-value	6.79 [0.37, 125.88], 0.1405		0.78 [0.19, 3.14], 0.7239		1.63 [0.50, 5.35], 0.4185	
RD [95%-CI]; p-value	0.09 [-0.00, 0.17], 0.0612		-0.03 [-0.17, 0.12], 0.7293		0.04 [-0.05, 0.12], 0.3917	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	12/82 (14.6)	6/42 (14.3)	5/94 (5.3)	3/40 (7.5)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	1.02 [0.41, 2.54], 0.9585		0.71 [0.18, 2.83], 0.6262		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	1.03 [0.36, 2.97], 0.9584		0.69 [0.16, 3.05], 0.6259		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	0.00 [-0.13, 0.13], 0.9583		-0.02 [-0.12, 0.07], 0.6472		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.1929		0.4601		0.7152	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	11/59 (18.6)	2/30 (6.7)	9/50 (18.0)	7/32 (21.9)	20/109 (18.3)	9/62 (14.5)
RR [95%-CI]; p-value	2.80 [0.66, 11.82], 0.1619		0.82 [0.34, 1.99], 0.6650		1.26 [0.61, 2.60], 0.5249	
OR [95%-CI]; p-value	3.21 [0.66, 15.53], 0.1304		0.78 [0.26, 2.37], 0.6658		1.32 [0.56, 3.12], 0.5209	
RD [95%-CI]; p-value	0.12 [-0.01, 0.25], 0.0788		-0.04 [-0.22, 0.14], 0.6705		0.04 [-0.08, 0.15], 0.5095	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	19/82 (23.2)	10/42 (23.8)	13/94 (13.8)	4/40 (10.0)	32/176 (18.2)	14/82 (17.1)
RR [95%-CI]; p-value	0.97 [0.50, 1.90], 0.9365		1.38 [0.48, 3.98], 0.5480		1.06 [0.60, 1.88], 0.8290	
OR [95%-CI]; p-value	0.97 [0.40, 2.32], 0.9366		1.44 [0.44, 4.74], 0.5422		1.08 [0.54, 2.15], 0.8285	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.15], 0.9368		0.04 [-0.08, 0.15], 0.5185		0.01 [-0.09, 0.11], 0.8270	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9445		0.1812		0.2216	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	3/59 (5.1)	1/30 (3.3)	6/50 (12.0)	4/32 (12.5)	9/109 (8.3)	5/62 (8.1)
RR [95%-CI]; p-value	1.53 [0.17, 14.05], 0.7093		0.96 [0.29, 3.14], 0.9462		1.02 [0.36, 2.92], 0.9648	
OR [95%-CI]; p-value	1.55 [0.15, 15.61], 0.7062		0.95 [0.25, 3.69], 0.9462		1.03 [0.33, 3.21], 0.9648	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6872		-0.01 [-0.15, 0.14], 0.9464		0.00 [-0.08, 0.09], 0.9647	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	13/82 (15.9)	4/42 (9.5)	9/94 (9.6)	0/40 (0.0)	22/176 (12.5)	4/82 (4.9)
RR [95%-CI]; p-value	1.66 [0.58, 4.79], 0.3448		7.76 [0.46, 130.61], 0.1551		2.56 [0.91, 7.20], 0.0741	
OR [95%-CI]; p-value	1.79 [0.55, 5.87], 0.3321		8.47 [0.48, 149.76], 0.0833		2.79 [0.93, 8.37], 0.0583	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.2966		0.08 [0.01, 0.15], 0.0170		0.08 [0.01, 0.14], 0.0270	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.7704		0.3169		0.2523	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	0/30 (0.0)	3/50 (6.0)	3/32 (9.4)	4/109 (3.7)	3/62 (4.8)
RR [95%-CI]; p-value	1.03 [0.04, 29.96], 0.9845		0.64 [0.14, 2.98], 0.5694		0.76 [0.18, 3.28], 0.7112	
OR [95%-CI]; p-value	1.03 [0.03, 31.73], 0.9845		0.62 [0.12, 3.26], 0.5670		0.75 [0.16, 3.46], 0.7107	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9844		-0.03 [-0.15, 0.09], 0.5832		-0.01 [-0.08, 0.05], 0.7204	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	7/82 (8.5)	2/42 (4.8)	4/94 (4.3)	0/40 (0.0)	11/176 (6.3)	2/82 (2.4)
RR [95%-CI]; p-value	1.79 [0.39, 8.25], 0.4537		3.45 [0.19, 63.70], 0.4057		2.56 [0.58, 11.30], 0.2138	
OR [95%-CI]; p-value	1.87 [0.37, 9.41], 0.4432		3.56 [0.18, 68.85], 0.3715		2.67 [0.58, 12.32], 0.1926	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4024		0.03 [-0.02, 0.08], 0.2650		0.04 [-0.01, 0.09], 0.1268	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.9965		0.6373		0.7642	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	0/30 (0.0)	1/50 (2.0)	1/32 (3.1)	2/109 (1.8)	1/62 (1.6)
RR [95%-CI]; p-value	1.03 [0.04, 29.96], 0.9845		0.64 [0.04, 9.87], 0.7492		1.14 [0.11, 12.29], 0.9154	
OR [95%-CI]; p-value	1.03 [0.03, 31.73], 0.9845		0.63 [0.04, 10.49], 0.7473		1.14 [0.10, 12.83], 0.9154	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9844		-0.01 [-0.08, 0.06], 0.7584		0.00 [-0.04, 0.04], 0.9139	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	2/82 (2.4)	1/42 (2.4)	2/94 (2.1)	0/40 (0.0)	4/176 (2.3)	1/82 (1.2)
RR [95%-CI]; p-value	1.02 [0.10, 10.97], 0.9841		1.72 [0.08, 37.39], 0.7288		1.86 [0.21, 16.41], 0.5749	
OR [95%-CI]; p-value	1.03 [0.09, 11.64], 0.9841		1.74 [0.08, 39.43], 0.7250		1.88 [0.21, 17.12], 0.5677	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9840		0.01 [-0.04, 0.05], 0.6960		0.01 [-0.02, 0.04], 0.5239	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.3468		0.4116		0.8568	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	37/59 (62.7)	20/30 (66.7)	23/50 (46.0)	17/32 (53.1)	60/109 (55.0)	37/62 (59.7)
RR [95%-CI]; p-value	0.94 [0.68, 1.30], 0.7084		0.87 [0.56, 1.35], 0.5239		0.92 [0.71, 1.20], 0.5514	
OR [95%-CI]; p-value	0.84 [0.33, 2.12], 0.7132		0.75 [0.31, 1.83], 0.5289		0.83 [0.44, 1.56], 0.5568	
RD [95%-CI]; p-value	-0.04 [-0.25, 0.17], 0.7107		-0.07 [-0.29, 0.15], 0.5280		-0.05 [-0.20, 0.11], 0.5548	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	45/82 (54.9)	30/42 (71.4)	47/94 (50.0)	18/40 (45.0)	92/176 (52.3)	48/82 (58.5)
RR [95%-CI]; p-value	0.77 [0.58, 1.01], 0.0594		1.11 [0.75, 1.65], 0.6037		0.89 [0.71, 1.12], 0.3358	
OR [95%-CI]; p-value	0.49 [0.22, 1.08], 0.0744		1.22 [0.58, 2.57], 0.5961		0.78 [0.46, 1.32], 0.3470	
RD [95%-CI]; p-value	-0.17 [-0.34, 0.01], 0.0622		0.05 [-0.13, 0.23], 0.5950		-0.06 [-0.19, 0.07], 0.3438	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.1462		0.9378		0.4282	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	16/59 (27.1)	13/30 (43.3)	20/50 (40.0)	9/32 (28.1)	36/109 (33.0)	22/62 (35.5)
RR [95%-CI]; p-value	0.63 [0.35, 1.12], 0.1165		1.42 [0.74, 2.72], 0.2879		0.93 [0.61, 1.43], 0.7432	
OR [95%-CI]; p-value	0.49 [0.19, 1.22], 0.1229		1.70 [0.65, 4.43], 0.2726		0.90 [0.47, 1.73], 0.7443	
RD [95%-CI]; p-value	-0.16 [-0.37, 0.05], 0.1311		0.12 [-0.09, 0.33], 0.2601		-0.02 [-0.17, 0.12], 0.7454	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	34/82 (41.5)	16/42 (38.1)	29/94 (30.9)	9/40 (22.5)	63/176 (35.8)	25/82 (30.5)
RR [95%-CI]; p-value	1.09 [0.68, 1.73], 0.7201		1.37 [0.72, 2.63], 0.3411		1.17 [0.80, 1.72], 0.4103	
OR [95%-CI]; p-value	1.15 [0.54, 2.47], 0.7175		1.54 [0.65, 3.64], 0.3264		1.27 [0.72, 2.23], 0.4024	
RD [95%-CI]; p-value	0.03 [-0.15, 0.22], 0.7161		0.08 [-0.08, 0.24], 0.3050		0.05 [-0.07, 0.18], 0.3948	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.3.1.s1
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.2381		0.8988		0.4003	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	0/30 (0.0)	5/50 (10.0)	4/32 (12.5)	11/109 (10.1)	4/62 (6.5)
RR [95%-CI]; p-value	6.20 [0.36, 107.42], 0.2097		0.80 [0.23, 2.76], 0.7238		1.56 [0.52, 4.70], 0.4258	
OR [95%-CI]; p-value	6.79 [0.37, 125.88], 0.1405		0.78 [0.19, 3.14], 0.7239		1.63 [0.50, 5.35], 0.4185	
RD [95%-CI]; p-value	0.09 [-0.00, 0.17], 0.0612		-0.03 [-0.17, 0.12], 0.7293		0.04 [-0.05, 0.12], 0.3917	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	12/82 (14.6)	6/42 (14.3)	5/94 (5.3)	3/40 (7.5)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	1.02 [0.41, 2.54], 0.9585		0.71 [0.18, 2.83], 0.6262		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	1.03 [0.36, 2.97], 0.9584		0.69 [0.16, 3.05], 0.6259		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	0.00 [-0.13, 0.13], 0.9583		-0.02 [-0.12, 0.07], 0.6472		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_3_1_m_sf_ttl_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1373		0.3747		0.5296	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	2/50 (4.0)	2/32 (6.3)	8/109 (7.3)	4/62 (6.5)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		0.64 [0.09, 4.32], 0.6468		1.14 [0.36, 3.63], 0.8274	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		0.63 [0.08, 4.68], 0.6445		1.15 [0.33, 3.98], 0.8270	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		-0.02 [-0.12, 0.08], 0.6590		0.01 [-0.07, 0.09], 0.8242	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	7/42 (16.7)	9/94 (9.6)	2/40 (5.0)	14/176 (8.0)	9/82 (11.0)
RR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0695		1.91 [0.43, 8.47], 0.3918		0.72 [0.33, 1.61], 0.4276	
OR [95%-CI]; p-value	0.32 [0.10, 1.09], 0.0596		2.01 [0.41, 9.76], 0.3774		0.70 [0.29, 1.69], 0.4278	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.02], 0.0949		0.05 [-0.04, 0.14], 0.3191		-0.03 [-0.11, 0.05], 0.4512	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1800		0.1278		0.1434	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	8/59 (13.6)	9/30 (30.0)	11/50 (22.0)	6/32 (18.8)	19/109 (17.4)	15/62 (24.2)
RR [95%-CI]; p-value	0.45 [0.19, 1.05], 0.0654		1.17 [0.48, 2.86], 0.7249		0.72 [0.40, 1.31], 0.2849	
OR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0622		1.22 [0.40, 3.71], 0.7232		0.66 [0.31, 1.42], 0.2868	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0829		0.03 [-0.14, 0.21], 0.7195		-0.07 [-0.20, 0.06], 0.3012	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	20/82 (24.4)	11/42 (26.2)	15/94 (16.0)	1/40 (2.5)	35/176 (19.9)	12/82 (14.6)
RR [95%-CI]; p-value	0.93 [0.49, 1.76], 0.8260		6.38 [0.87, 46.70], 0.0679		1.36 [0.75, 2.48], 0.3173	
OR [95%-CI]; p-value	0.91 [0.39, 2.13], 0.8266		7.41 [0.94, 58.12], 0.0279		1.45 [0.71, 2.96], 0.3088	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.14], 0.8278		0.13 [0.05, 0.22], 0.0029		0.05 [-0.04, 0.15], 0.2865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9734		0.7041		0.8371	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	9/59 (15.3)	7/30 (23.3)	5/50 (10.0)	5/32 (15.6)	14/109 (12.8)	12/62 (19.4)
RR [95%-CI]; p-value	0.65 [0.27, 1.58], 0.3463		0.64 [0.20, 2.04], 0.4498		0.66 [0.33, 1.34], 0.2544	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3481		0.60 [0.16, 2.26], 0.4477		0.61 [0.26, 1.43], 0.2543	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3709		-0.06 [-0.21, 0.09], 0.4647		-0.07 [-0.18, 0.05], 0.2741	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	8/42 (19.0)	12/94 (12.8)	6/40 (15.0)	22/176 (12.5)	14/82 (17.1)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3050		0.85 [0.34, 2.11], 0.7276		0.73 [0.40, 1.36], 0.3217	
OR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3053		0.83 [0.29, 2.39], 0.7286		0.69 [0.33, 1.44], 0.3236	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3314		-0.02 [-0.15, 0.11], 0.7355		-0.05 [-0.14, 0.05], 0.3453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1273		0.6134		0.1585	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	16/59 (27.1)	12/30 (40.0)	13/50 (26.0)	9/32 (28.1)	29/109 (26.6)	21/62 (33.9)
RR [95%-CI]; p-value	0.68 [0.37, 1.24], 0.2086		0.92 [0.45, 1.91], 0.8318		0.79 [0.49, 1.25], 0.3110	
OR [95%-CI]; p-value	0.56 [0.22, 1.41], 0.2161		0.90 [0.33, 2.43], 0.8322		0.71 [0.36, 1.39], 0.3153	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.08], 0.2266		-0.02 [-0.22, 0.18], 0.8331		-0.07 [-0.22, 0.07], 0.3230	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	22/82 (26.8)	8/42 (19.0)	20/94 (21.3)	7/40 (17.5)	42/176 (23.9)	15/82 (18.3)
RR [95%-CI]; p-value	1.41 [0.69, 2.89], 0.3502		1.22 [0.56, 2.64], 0.6221		1.30 [0.77, 2.21], 0.3238	
OR [95%-CI]; p-value	1.56 [0.63, 3.88], 0.3383		1.27 [0.49, 3.31], 0.6180		1.40 [0.72, 2.70], 0.3152	
RD [95%-CI]; p-value	0.08 [-0.07, 0.23], 0.3177		0.04 [-0.11, 0.18], 0.6070		0.06 [-0.05, 0.16], 0.2971	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8356		0.9298		0.9637	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	3/50 (6.0)	1/32 (3.1)	9/109 (8.3)	3/62 (4.8)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		1.92 [0.21, 17.66], 0.5645		1.71 [0.48, 6.07], 0.4091	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		1.98 [0.20, 19.90], 0.5555		1.77 [0.46, 6.80], 0.4002	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		0.03 [-0.06, 0.12], 0.5279		0.03 [-0.04, 0.11], 0.3673	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	11/82 (13.4)	3/42 (7.1)	8/94 (8.5)	2/40 (5.0)	19/176 (10.8)	5/82 (6.1)
RR [95%-CI]; p-value	1.88 [0.55, 6.37], 0.3118		1.70 [0.38, 7.66], 0.4884		1.77 [0.68, 4.58], 0.2384	
OR [95%-CI]; p-value	2.01 [0.53, 7.65], 0.2963		1.77 [0.36, 8.72], 0.4792		1.86 [0.67, 5.18], 0.2264	
RD [95%-CI]; p-value	0.06 [-0.04, 0.17], 0.2518		0.04 [-0.05, 0.12], 0.4343		0.05 [-0.02, 0.12], 0.1831	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1325		0.6030		0.3912	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	10/59 (16.9)	3/30 (10.0)	5/50 (10.0)	4/32 (12.5)	15/109 (13.8)	7/62 (11.3)
RR [95%-CI]; p-value	1.69 [0.50, 5.70], 0.3939		0.80 [0.23, 2.76], 0.7238		1.22 [0.53, 2.83], 0.6447	
OR [95%-CI]; p-value	1.84 [0.47, 7.25], 0.3802		0.78 [0.19, 3.14], 0.7239		1.25 [0.48, 3.26], 0.6427	
RD [95%-CI]; p-value	0.07 [-0.07, 0.21], 0.3437		-0.03 [-0.17, 0.12], 0.7293		0.02 [-0.08, 0.13], 0.6346	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	7/82 (8.5)	7/42 (16.7)	9/94 (9.6)	3/40 (7.5)	16/176 (9.1)	10/82 (12.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.36], 0.1806		1.28 [0.36, 4.47], 0.7025		0.75 [0.35, 1.57], 0.4398	
OR [95%-CI]; p-value	0.47 [0.15, 1.43], 0.1758		1.31 [0.33, 5.10], 0.7004		0.72 [0.31, 1.66], 0.4406	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2128		0.02 [-0.08, 0.12], 0.6873		-0.03 [-0.11, 0.05], 0.4613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6345		0.6370		0.4541	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	11/59 (18.6)	7/30 (23.3)	9/50 (18.0)	5/32 (15.6)	20/109 (18.3)	12/62 (19.4)
RR [95%-CI]; p-value	0.80 [0.35, 1.85], 0.6004		1.15 [0.42, 3.13], 0.7813		0.95 [0.50, 1.81], 0.8710	
OR [95%-CI]; p-value	0.75 [0.26, 2.20], 0.6026		1.19 [0.36, 3.92], 0.7804		0.94 [0.42, 2.07], 0.8712	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.6117		0.02 [-0.14, 0.19], 0.7776		-0.01 [-0.13, 0.11], 0.8719	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	17/82 (20.7)	14/42 (33.3)	16/94 (17.0)	8/40 (20.0)	33/176 (18.8)	22/82 (26.8)
RR [95%-CI]; p-value	0.62 [0.34, 1.14], 0.1219		0.85 [0.40, 1.83], 0.6790		0.70 [0.44, 1.12], 0.1364	
OR [95%-CI]; p-value	0.52 [0.23, 1.21], 0.1251		0.82 [0.32, 2.11], 0.6807		0.63 [0.34, 1.17], 0.1401	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1401		-0.03 [-0.18, 0.12], 0.6880		-0.08 [-0.19, 0.03], 0.1570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2393		0.9821		0.4212	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	9/30 (30.0)	6/50 (12.0)	5/32 (15.6)	12/109 (11.0)	14/62 (22.6)
RR [95%-CI]; p-value	0.34 [0.13, 0.86], 0.0233		0.77 [0.26, 2.31], 0.6383		0.49 [0.24, 0.99], 0.0459	
OR [95%-CI]; p-value	0.26 [0.08, 0.83], 0.0182		0.74 [0.20, 2.65], 0.6385		0.42 [0.18, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.20 [-0.38, -0.02], 0.0320		-0.04 [-0.19, 0.12], 0.6461		-0.12 [-0.24, 0.00], 0.0577	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	18/82 (22.0)	14/42 (33.3)	16/94 (17.0)	9/40 (22.5)	34/176 (19.3)	23/82 (28.0)
RR [95%-CI]; p-value	0.66 [0.36, 1.19], 0.1661		0.76 [0.37, 1.57], 0.4525		0.69 [0.43, 1.09], 0.1119	
OR [95%-CI]; p-value	0.56 [0.25, 1.29], 0.1704		0.71 [0.28, 1.77], 0.4563		0.61 [0.33, 1.13], 0.1155	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.05], 0.1852		-0.05 [-0.20, 0.10], 0.4742		-0.09 [-0.20, 0.03], 0.1313	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.8439		0.5300		0.7790	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	6/30 (20.0)	8/50 (16.0)	5/32 (15.6)	14/109 (12.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.51 [0.18, 1.44], 0.2036		1.02 [0.37, 2.86], 0.9638		0.72 [0.35, 1.50], 0.3828	
OR [95%-CI]; p-value	0.45 [0.13, 1.55], 0.1993		1.03 [0.30, 3.48], 0.9638		0.68 [0.29, 1.61], 0.3835	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2360		0.00 [-0.16, 0.17], 0.9637		-0.05 [-0.16, 0.06], 0.3996	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	7/42 (16.7)	12/94 (12.8)	3/40 (7.5)	18/176 (10.2)	10/82 (12.2)
RR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1155		1.70 [0.51, 5.71], 0.3889		0.84 [0.41, 1.74], 0.6353	
OR [95%-CI]; p-value	0.39 [0.12, 1.26], 0.1077		1.80 [0.48, 6.78], 0.3763		0.82 [0.36, 1.87], 0.6361	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1459		0.05 [-0.05, 0.16], 0.3297		-0.02 [-0.10, 0.06], 0.6453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8647		0.9177		0.7386	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	3/30 (10.0)	6/50 (12.0)	3/32 (9.4)	11/109 (10.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.85 [0.22, 3.31], 0.8118		1.28 [0.34, 4.76], 0.7125		1.04 [0.41, 2.68], 0.9307	
OR [95%-CI]; p-value	0.83 [0.19, 3.75], 0.8120		1.32 [0.31, 5.69], 0.7107		1.05 [0.37, 2.99], 0.9306	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8164		0.03 [-0.11, 0.16], 0.7038		0.00 [-0.09, 0.10], 0.9303	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	13/82 (15.9)	9/42 (21.4)	11/94 (11.7)	4/40 (10.0)	24/176 (13.6)	13/82 (15.9)
RR [95%-CI]; p-value	0.74 [0.34, 1.59], 0.4396		1.17 [0.40, 3.46], 0.7760		0.86 [0.46, 1.60], 0.6350	
OR [95%-CI]; p-value	0.69 [0.27, 1.78], 0.4418		1.19 [0.36, 4.00], 0.7749		0.84 [0.40, 1.74], 0.6361	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.09], 0.4577		0.02 [-0.10, 0.13], 0.7687		-0.02 [-0.12, 0.07], 0.6436	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9936		0.7839		0.6691	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	4/59 (6.8)	4/30 (13.3)	3/50 (6.0)	2/32 (6.3)	7/109 (6.4)	6/62 (9.7)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3132		0.96 [0.17, 5.43], 0.9632		0.66 [0.23, 1.89], 0.4418	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3069		0.96 [0.15, 6.07], 0.9632		0.64 [0.21, 2.00], 0.4400	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3503		-0.00 [-0.11, 0.10], 0.9633		-0.03 [-0.12, 0.05], 0.4623	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	5/42 (11.9)	12/94 (12.8)	4/40 (10.0)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	0.51 [0.16, 1.67], 0.2675		1.28 [0.44, 3.72], 0.6545		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	0.48 [0.13, 1.76], 0.2610		1.32 [0.40, 4.36], 0.6514		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.3043		0.03 [-0.09, 0.14], 0.6370		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.1.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.0990		0.9469		0.2086	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	6/30 (20.0)	5/50 (10.0)	4/32 (12.5)	10/109 (9.2)	10/62 (16.1)
RR [95%-CI]; p-value	0.42 [0.14, 1.28], 0.1269		0.80 [0.23, 2.76], 0.7238		0.57 [0.25, 1.29], 0.1770	
OR [95%-CI]; p-value	0.37 [0.10, 1.33], 0.1184		0.78 [0.19, 3.14], 0.7239		0.53 [0.21, 1.34], 0.1737	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1575		-0.03 [-0.17, 0.12], 0.7293		-0.07 [-0.18, 0.04], 0.2001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	3/42 (7.1)	6/94 (6.4)	3/40 (7.5)	16/176 (9.1)	6/82 (7.3)
RR [95%-CI]; p-value	1.71 [0.50, 5.87], 0.3961		0.85 [0.22, 3.24], 0.8129		1.24 [0.50, 3.06], 0.6368	
OR [95%-CI]; p-value	1.81 [0.47, 6.95], 0.3848		0.84 [0.20, 3.54], 0.8131		1.27 [0.48, 3.37], 0.6348	
RD [95%-CI]; p-value	0.05 [-0.05, 0.16], 0.3469		-0.01 [-0.11, 0.08], 0.8185		0.02 [-0.05, 0.09], 0.6223	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_1_m_soc_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.3.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3014		0.8476		0.5548	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	7/30 (23.3)	3/50 (6.0)	0/32 (0.0)	5/109 (4.6)	7/62 (11.3)
RR [95%-CI]; p-value	0.15 [0.03, 0.66], 0.0122		3.90 [0.20, 75.35], 0.3677		0.41 [0.13, 1.23], 0.1100	
OR [95%-CI]; p-value	0.12 [0.02, 0.60], 0.0032		4.09 [0.20, 84.33], 0.3259		0.38 [0.11, 1.25], 0.0990	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0135		0.04 [-0.03, 0.12], 0.2638		-0.07 [-0.16, 0.02], 0.1356	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	4/82 (4.9)	5/42 (11.9)	3/94 (3.2)	0/40 (0.0)	7/176 (4.0)	5/82 (6.1)
RR [95%-CI]; p-value	0.41 [0.12, 1.45], 0.1656		2.59 [0.13, 50.45], 0.5310		0.65 [0.21, 1.99], 0.4535	
OR [95%-CI]; p-value	0.38 [0.10, 1.50], 0.1535		2.64 [0.13, 53.88], 0.5131		0.64 [0.20, 2.07], 0.4514	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2042		0.02 [-0.03, 0.07], 0.4355		-0.02 [-0.08, 0.04], 0.4834	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_3_m_pt_ae10pct_age.sas using SAS 9.4

Table 12.4.4.1.3.s1
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2547		0.4086		0.2552	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	4/30 (13.3)	2/50 (4.0)	2/32 (6.3)	3/109 (2.8)	6/62 (9.7)
RR [95%-CI]; p-value	0.13 [0.01, 1.09], 0.0597		0.64 [0.09, 4.32], 0.6468		0.28 [0.07, 1.10], 0.0680	
OR [95%-CI]; p-value	0.11 [0.01, 1.05], 0.0242		0.63 [0.08, 4.68], 0.6445		0.26 [0.06, 1.10], 0.0512	
RD [95%-CI]; p-value	-0.12 [-0.24, 0.01], 0.0703		-0.02 [-0.12, 0.08], 0.6590		-0.07 [-0.15, 0.01], 0.0887	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	6/42 (14.3)	5/94 (5.3)	1/40 (2.5)	11/176 (6.3)	7/82 (8.5)
RR [95%-CI]; p-value	0.51 [0.18, 1.49], 0.2198		2.13 [0.26, 17.64], 0.4841		0.73 [0.29, 1.82], 0.5022	
OR [95%-CI]; p-value	0.47 [0.14, 1.57], 0.2142		2.19 [0.25, 19.38], 0.4702		0.71 [0.27, 1.91], 0.5020	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2547		0.03 [-0.04, 0.09], 0.4048		-0.02 [-0.09, 0.05], 0.5236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_3_m_pt_ae10pct_age.sas using SAS 9.4

Table 12.4.8.1.1.s1
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2654		0.5725		0.1119	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	0/59 (0.0)	1/30 (3.3)	3/50 (6.0)	3/32 (9.4)	3/109 (2.8)	4/62 (6.5)
RR [95%-CI]; p-value	0.25 [0.01, 7.30], 0.4224		0.64 [0.14, 2.98], 0.5694		0.43 [0.10, 1.84], 0.2541	
OR [95%-CI]; p-value	0.25 [0.01, 7.54], 0.3858		0.62 [0.12, 3.26], 0.5670		0.41 [0.09, 1.90], 0.2405	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.04], 0.4743		-0.03 [-0.15, 0.09], 0.5832		-0.04 [-0.11, 0.03], 0.2894	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	8/82 (9.8)	2/42 (4.8)	2/94 (2.1)	0/40 (0.0)	10/176 (5.7)	2/82 (2.4)
RR [95%-CI]; p-value	2.05 [0.46, 9.22], 0.3500		1.72 [0.08, 37.39], 0.7288		2.33 [0.52, 10.39], 0.2677	
OR [95%-CI]; p-value	2.16 [0.44, 10.67], 0.3337		1.74 [0.08, 39.43], 0.7250		2.41 [0.52, 11.26], 0.2494	
RD [95%-CI]; p-value	0.05 [-0.04, 0.14], 0.2818		0.01 [-0.04, 0.05], 0.6960		0.03 [-0.02, 0.08], 0.1836	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_8_1_1_m_soc_sae5pct_age.sas using SAS 9.4

Table 12.4.8.1.2.s1
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_8_1_2_m_pt_sae5pct_age.sas using SAS 9.4

Table 12.4.5.1.1.s1
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_5_1_1_m_soc_aeg35pct_age.sas using SAS 9.4

Table 12.4.5.1.2.s1
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_5_1_2_m_pt_aeg35pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1373		0.3747		0.5296	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	2/50 (4.0)	2/32 (6.3)	8/109 (7.3)	4/62 (6.5)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		0.64 [0.09, 4.32], 0.6468		1.14 [0.36, 3.63], 0.8274	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		0.63 [0.08, 4.68], 0.6445		1.15 [0.33, 3.98], 0.8270	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		-0.02 [-0.12, 0.08], 0.6590		0.01 [-0.07, 0.09], 0.8242	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	7/42 (16.7)	9/94 (9.6)	2/40 (5.0)	14/176 (8.0)	9/82 (11.0)
RR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0695		1.91 [0.43, 8.47], 0.3918		0.72 [0.33, 1.61], 0.4276	
OR [95%-CI]; p-value	0.32 [0.10, 1.09], 0.0596		2.01 [0.41, 9.76], 0.3774		0.70 [0.29, 1.69], 0.4278	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.02], 0.0949		0.05 [-0.04, 0.14], 0.3191		-0.03 [-0.11, 0.05], 0.4512	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1800		0.1278		0.1434	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	8/59 (13.6)	9/30 (30.0)	11/50 (22.0)	6/32 (18.8)	19/109 (17.4)	15/62 (24.2)
RR [95%-CI]; p-value	0.45 [0.19, 1.05], 0.0654		1.17 [0.48, 2.86], 0.7249		0.72 [0.40, 1.31], 0.2849	
OR [95%-CI]; p-value	0.37 [0.12, 1.08], 0.0622		1.22 [0.40, 3.71], 0.7232		0.66 [0.31, 1.42], 0.2868	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0829		0.03 [-0.14, 0.21], 0.7195		-0.07 [-0.20, 0.06], 0.3012	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	20/82 (24.4)	11/42 (26.2)	15/94 (16.0)	1/40 (2.5)	35/176 (19.9)	12/82 (14.6)
RR [95%-CI]; p-value	0.93 [0.49, 1.76], 0.8260		6.38 [0.87, 46.70], 0.0679		1.36 [0.75, 2.48], 0.3173	
OR [95%-CI]; p-value	0.91 [0.39, 2.13], 0.8266		7.41 [0.94, 58.12], 0.0279		1.45 [0.71, 2.96], 0.3088	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.14], 0.8278		0.13 [0.05, 0.22], 0.0029		0.05 [-0.04, 0.15], 0.2865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9734		0.7041		0.8371	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	9/59 (15.3)	7/30 (23.3)	5/50 (10.0)	5/32 (15.6)	14/109 (12.8)	12/62 (19.4)
RR [95%-CI]; p-value	0.65 [0.27, 1.58], 0.3463		0.64 [0.20, 2.04], 0.4498		0.66 [0.33, 1.34], 0.2544	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3481		0.60 [0.16, 2.26], 0.4477		0.61 [0.26, 1.43], 0.2543	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3709		-0.06 [-0.21, 0.09], 0.4647		-0.07 [-0.18, 0.05], 0.2741	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	8/42 (19.0)	12/94 (12.8)	6/40 (15.0)	22/176 (12.5)	14/82 (17.1)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3050		0.85 [0.34, 2.11], 0.7276		0.73 [0.40, 1.36], 0.3217	
OR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3053		0.83 [0.29, 2.39], 0.7286		0.69 [0.33, 1.44], 0.3236	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3314		-0.02 [-0.15, 0.11], 0.7355		-0.05 [-0.14, 0.05], 0.3453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1273		0.6134		0.1585	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	16/59 (27.1)	12/30 (40.0)	13/50 (26.0)	9/32 (28.1)	29/109 (26.6)	21/62 (33.9)
RR [95%-CI]; p-value	0.68 [0.37, 1.24], 0.2086		0.92 [0.45, 1.91], 0.8318		0.79 [0.49, 1.25], 0.3110	
OR [95%-CI]; p-value	0.56 [0.22, 1.41], 0.2161		0.90 [0.33, 2.43], 0.8322		0.71 [0.36, 1.39], 0.3153	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.08], 0.2266		-0.02 [-0.22, 0.18], 0.8331		-0.07 [-0.22, 0.07], 0.3230	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	22/82 (26.8)	8/42 (19.0)	20/94 (21.3)	7/40 (17.5)	42/176 (23.9)	15/82 (18.3)
RR [95%-CI]; p-value	1.41 [0.69, 2.89], 0.3502		1.22 [0.56, 2.64], 0.6221		1.30 [0.77, 2.21], 0.3238	
OR [95%-CI]; p-value	1.56 [0.63, 3.88], 0.3383		1.27 [0.49, 3.31], 0.6180		1.40 [0.72, 2.70], 0.3152	
RD [95%-CI]; p-value	0.08 [-0.07, 0.23], 0.3177		0.04 [-0.11, 0.18], 0.6070		0.06 [-0.05, 0.16], 0.2971	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8356		0.9298		0.9637	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	2/30 (6.7)	3/50 (6.0)	1/32 (3.1)	9/109 (8.3)	3/62 (4.8)
RR [95%-CI]; p-value	1.53 [0.33, 7.11], 0.5907		1.92 [0.21, 17.66], 0.5645		1.71 [0.48, 6.07], 0.4091	
OR [95%-CI]; p-value	1.58 [0.30, 8.37], 0.5850		1.98 [0.20, 19.90], 0.5555		1.77 [0.46, 6.80], 0.4002	
RD [95%-CI]; p-value	0.04 [-0.08, 0.15], 0.5606		0.03 [-0.06, 0.12], 0.5279		0.03 [-0.04, 0.11], 0.3673	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	11/82 (13.4)	3/42 (7.1)	8/94 (8.5)	2/40 (5.0)	19/176 (10.8)	5/82 (6.1)
RR [95%-CI]; p-value	1.88 [0.55, 6.37], 0.3118		1.70 [0.38, 7.66], 0.4884		1.77 [0.68, 4.58], 0.2384	
OR [95%-CI]; p-value	2.01 [0.53, 7.65], 0.2963		1.77 [0.36, 8.72], 0.4792		1.86 [0.67, 5.18], 0.2264	
RD [95%-CI]; p-value	0.06 [-0.04, 0.17], 0.2518		0.04 [-0.05, 0.12], 0.4343		0.05 [-0.02, 0.12], 0.1831	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1325		0.6030		0.3912	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	10/59 (16.9)	3/30 (10.0)	5/50 (10.0)	4/32 (12.5)	15/109 (13.8)	7/62 (11.3)
RR [95%-CI]; p-value	1.69 [0.50, 5.70], 0.3939		0.80 [0.23, 2.76], 0.7238		1.22 [0.53, 2.83], 0.6447	
OR [95%-CI]; p-value	1.84 [0.47, 7.25], 0.3802		0.78 [0.19, 3.14], 0.7239		1.25 [0.48, 3.26], 0.6427	
RD [95%-CI]; p-value	0.07 [-0.07, 0.21], 0.3437		-0.03 [-0.17, 0.12], 0.7293		0.02 [-0.08, 0.13], 0.6346	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	7/82 (8.5)	7/42 (16.7)	9/94 (9.6)	3/40 (7.5)	16/176 (9.1)	10/82 (12.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.36], 0.1806		1.28 [0.36, 4.47], 0.7025		0.75 [0.35, 1.57], 0.4398	
OR [95%-CI]; p-value	0.47 [0.15, 1.43], 0.1758		1.31 [0.33, 5.10], 0.7004		0.72 [0.31, 1.66], 0.4406	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2128		0.02 [-0.08, 0.12], 0.6873		-0.03 [-0.11, 0.05], 0.4613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6345		0.6370		0.4541	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	11/59 (18.6)	7/30 (23.3)	9/50 (18.0)	5/32 (15.6)	20/109 (18.3)	12/62 (19.4)
RR [95%-CI]; p-value	0.80 [0.35, 1.85], 0.6004		1.15 [0.42, 3.13], 0.7813		0.95 [0.50, 1.81], 0.8710	
OR [95%-CI]; p-value	0.75 [0.26, 2.20], 0.6026		1.19 [0.36, 3.92], 0.7804		0.94 [0.42, 2.07], 0.8712	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.6117		0.02 [-0.14, 0.19], 0.7776		-0.01 [-0.13, 0.11], 0.8719	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	17/82 (20.7)	14/42 (33.3)	16/94 (17.0)	8/40 (20.0)	33/176 (18.8)	22/82 (26.8)
RR [95%-CI]; p-value	0.62 [0.34, 1.14], 0.1219		0.85 [0.40, 1.83], 0.6790		0.70 [0.44, 1.12], 0.1364	
OR [95%-CI]; p-value	0.52 [0.23, 1.21], 0.1251		0.82 [0.32, 2.11], 0.6807		0.63 [0.34, 1.17], 0.1401	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1401		-0.03 [-0.18, 0.12], 0.6880		-0.08 [-0.19, 0.03], 0.1570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2393		0.9821		0.4212	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	9/30 (30.0)	6/50 (12.0)	5/32 (15.6)	12/109 (11.0)	14/62 (22.6)
RR [95%-CI]; p-value	0.34 [0.13, 0.86], 0.0233		0.77 [0.26, 2.31], 0.6383		0.49 [0.24, 0.99], 0.0459	
OR [95%-CI]; p-value	0.26 [0.08, 0.83], 0.0182		0.74 [0.20, 2.65], 0.6385		0.42 [0.18, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.20 [-0.38, -0.02], 0.0320		-0.04 [-0.19, 0.12], 0.6461		-0.12 [-0.24, 0.00], 0.0577	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	18/82 (22.0)	14/42 (33.3)	16/94 (17.0)	9/40 (22.5)	34/176 (19.3)	23/82 (28.0)
RR [95%-CI]; p-value	0.66 [0.36, 1.19], 0.1661		0.76 [0.37, 1.57], 0.4525		0.69 [0.43, 1.09], 0.1119	
OR [95%-CI]; p-value	0.56 [0.25, 1.29], 0.1704		0.71 [0.28, 1.77], 0.4563		0.61 [0.33, 1.13], 0.1155	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.05], 0.1852		-0.05 [-0.20, 0.10], 0.4742		-0.09 [-0.20, 0.03], 0.1313	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.8439		0.5300		0.7790	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	6/30 (20.0)	8/50 (16.0)	5/32 (15.6)	14/109 (12.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.51 [0.18, 1.44], 0.2036		1.02 [0.37, 2.86], 0.9638		0.72 [0.35, 1.50], 0.3828	
OR [95%-CI]; p-value	0.45 [0.13, 1.55], 0.1993		1.03 [0.30, 3.48], 0.9638		0.68 [0.29, 1.61], 0.3835	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2360		0.00 [-0.16, 0.17], 0.9637		-0.05 [-0.16, 0.06], 0.3996	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	7/42 (16.7)	12/94 (12.8)	3/40 (7.5)	18/176 (10.2)	10/82 (12.2)
RR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1155		1.70 [0.51, 5.71], 0.3889		0.84 [0.41, 1.74], 0.6353	
OR [95%-CI]; p-value	0.39 [0.12, 1.26], 0.1077		1.80 [0.48, 6.78], 0.3763		0.82 [0.36, 1.87], 0.6361	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1459		0.05 [-0.05, 0.16], 0.3297		-0.02 [-0.10, 0.06], 0.6453	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.2069		0.5396		0.6918	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	1/30 (3.3)	4/50 (8.0)	4/32 (12.5)	10/109 (9.2)	5/62 (8.1)
RR [95%-CI]; p-value	3.05 [0.38, 24.20], 0.2911		0.64 [0.17, 2.38], 0.5053		1.14 [0.41, 3.18], 0.8057	
OR [95%-CI]; p-value	3.28 [0.38, 28.61], 0.2574		0.61 [0.14, 2.63], 0.5029		1.15 [0.38, 3.54], 0.8052	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1819		-0.05 [-0.18, 0.09], 0.5199		0.01 [-0.08, 0.10], 0.8021	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	4/42 (9.5)	8/94 (8.5)	3/40 (7.5)	13/176 (7.4)	7/82 (8.5)
RR [95%-CI]; p-value	0.64 [0.18, 2.26], 0.4883		1.13 [0.32, 4.06], 0.8458		0.87 [0.36, 2.09], 0.7474	
OR [95%-CI]; p-value	0.62 [0.16, 2.43], 0.4864		1.15 [0.29, 4.57], 0.8454		0.85 [0.33, 2.23], 0.7477	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5135		0.01 [-0.09, 0.11], 0.8418		-0.01 [-0.08, 0.06], 0.7534	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8647		0.9177		0.7386	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	3/30 (10.0)	6/50 (12.0)	3/32 (9.4)	11/109 (10.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.85 [0.22, 3.31], 0.8118		1.28 [0.34, 4.76], 0.7125		1.04 [0.41, 2.68], 0.9307	
OR [95%-CI]; p-value	0.83 [0.19, 3.75], 0.8120		1.32 [0.31, 5.69], 0.7107		1.05 [0.37, 2.99], 0.9306	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8164		0.03 [-0.11, 0.16], 0.7038		0.00 [-0.09, 0.10], 0.9303	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	13/82 (15.9)	9/42 (21.4)	11/94 (11.7)	4/40 (10.0)	24/176 (13.6)	13/82 (15.9)
RR [95%-CI]; p-value	0.74 [0.34, 1.59], 0.4396		1.17 [0.40, 3.46], 0.7760		0.86 [0.46, 1.60], 0.6350	
OR [95%-CI]; p-value	0.69 [0.27, 1.78], 0.4418		1.19 [0.36, 4.00], 0.7749		0.84 [0.40, 1.74], 0.6361	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.09], 0.4577		0.02 [-0.10, 0.13], 0.7687		-0.02 [-0.12, 0.07], 0.6436	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9936		0.7839		0.6691	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	4/59 (6.8)	4/30 (13.3)	3/50 (6.0)	2/32 (6.3)	7/109 (6.4)	6/62 (9.7)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3132		0.96 [0.17, 5.43], 0.9632		0.66 [0.23, 1.89], 0.4418	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3069		0.96 [0.15, 6.07], 0.9632		0.64 [0.21, 2.00], 0.4400	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3503		-0.00 [-0.11, 0.10], 0.9633		-0.03 [-0.12, 0.05], 0.4623	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	5/42 (11.9)	12/94 (12.8)	4/40 (10.0)	17/176 (9.7)	9/82 (11.0)
RR [95%-CI]; p-value	0.51 [0.16, 1.67], 0.2675		1.28 [0.44, 3.72], 0.6545		0.88 [0.41, 1.89], 0.7432	
OR [95%-CI]; p-value	0.48 [0.13, 1.76], 0.2610		1.32 [0.40, 4.36], 0.6514		0.87 [0.37, 2.04], 0.7436	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.3043		0.03 [-0.09, 0.14], 0.6370		-0.01 [-0.09, 0.07], 0.7486	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.2.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.0990		0.9469		0.2086	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	5/59 (8.5)	6/30 (20.0)	5/50 (10.0)	4/32 (12.5)	10/109 (9.2)	10/62 (16.1)
RR [95%-CI]; p-value	0.42 [0.14, 1.28], 0.1269		0.80 [0.23, 2.76], 0.7238		0.57 [0.25, 1.29], 0.1770	
OR [95%-CI]; p-value	0.37 [0.10, 1.33], 0.1184		0.78 [0.19, 3.14], 0.7239		0.53 [0.21, 1.34], 0.1737	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1575		-0.03 [-0.17, 0.12], 0.7293		-0.07 [-0.18, 0.04], 0.2001	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	10/82 (12.2)	3/42 (7.1)	6/94 (6.4)	3/40 (7.5)	16/176 (9.1)	6/82 (7.3)
RR [95%-CI]; p-value	1.71 [0.50, 5.87], 0.3961		0.85 [0.22, 3.24], 0.8129		1.24 [0.50, 3.06], 0.6368	
OR [95%-CI]; p-value	1.81 [0.47, 6.95], 0.3848		0.84 [0.20, 3.54], 0.8131		1.27 [0.48, 3.37], 0.6348	
RD [95%-CI]; p-value	0.05 [-0.05, 0.16], 0.3469		-0.01 [-0.11, 0.08], 0.8185		0.02 [-0.05, 0.09], 0.6223	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_2_m_soc_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.4.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3014		0.8476		0.5548	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	7/30 (23.3)	3/50 (6.0)	0/32 (0.0)	5/109 (4.6)	7/62 (11.3)
RR [95%-CI]; p-value	0.15 [0.03, 0.66], 0.0122		3.90 [0.20, 75.35], 0.3677		0.41 [0.13, 1.23], 0.1100	
OR [95%-CI]; p-value	0.12 [0.02, 0.60], 0.0032		4.09 [0.20, 84.33], 0.3259		0.38 [0.11, 1.25], 0.0990	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0135		0.04 [-0.03, 0.12], 0.2638		-0.07 [-0.16, 0.02], 0.1356	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	4/82 (4.9)	5/42 (11.9)	3/94 (3.2)	0/40 (0.0)	7/176 (4.0)	5/82 (6.1)
RR [95%-CI]; p-value	0.41 [0.12, 1.45], 0.1656		2.59 [0.13, 50.45], 0.5310		0.65 [0.21, 1.99], 0.4535	
OR [95%-CI]; p-value	0.38 [0.10, 1.50], 0.1535		2.64 [0.13, 53.88], 0.5131		0.64 [0.20, 2.07], 0.4514	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2042		0.02 [-0.03, 0.07], 0.4355		-0.02 [-0.08, 0.04], 0.4834	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_4_m_pt_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.4.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2547		0.4086		0.2552	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	1/59 (1.7)	4/30 (13.3)	2/50 (4.0)	2/32 (6.3)	3/109 (2.8)	6/62 (9.7)
RR [95%-CI]; p-value	0.13 [0.01, 1.09], 0.0597		0.64 [0.09, 4.32], 0.6468		0.28 [0.07, 1.10], 0.0680	
OR [95%-CI]; p-value	0.11 [0.01, 1.05], 0.0242		0.63 [0.08, 4.68], 0.6445		0.26 [0.06, 1.10], 0.0512	
RD [95%-CI]; p-value	-0.12 [-0.24, 0.01], 0.0703		-0.02 [-0.12, 0.08], 0.6590		-0.07 [-0.15, 0.01], 0.0887	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	6/42 (14.3)	5/94 (5.3)	1/40 (2.5)	11/176 (6.3)	7/82 (8.5)
RR [95%-CI]; p-value	0.51 [0.18, 1.49], 0.2198		2.13 [0.26, 17.64], 0.4841		0.73 [0.29, 1.82], 0.5022	
OR [95%-CI]; p-value	0.47 [0.14, 1.57], 0.2142		2.19 [0.25, 19.38], 0.4702		0.71 [0.27, 1.91], 0.5020	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2547		0.03 [-0.04, 0.09], 0.4048		-0.02 [-0.09, 0.05], 0.5236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_4_m_pt_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.4.s1
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.1524		0.7916		0.2093	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	4/59 (6.8)	4/30 (13.3)	4/50 (8.0)	4/32 (12.5)	8/109 (7.3)	8/62 (12.9)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3132		0.64 [0.17, 2.38], 0.5053		0.57 [0.22, 1.44], 0.2339	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3069		0.61 [0.14, 2.63], 0.5029		0.53 [0.19, 1.50], 0.2297	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3503		-0.05 [-0.18, 0.09], 0.5199		-0.06 [-0.15, 0.04], 0.2597	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	1/42 (2.4)	4/94 (4.3)	2/40 (5.0)	10/176 (5.7)	3/82 (3.7)
RR [95%-CI]; p-value	3.07 [0.38, 24.70], 0.2910		0.85 [0.16, 4.46], 0.8487		1.55 [0.44, 5.49], 0.4946	
OR [95%-CI]; p-value	3.24 [0.38, 27.81], 0.2597		0.84 [0.15, 4.81], 0.8487		1.59 [0.42, 5.92], 0.4891	
RD [95%-CI]; p-value	0.05 [-0.02, 0.12], 0.1840		-0.01 [-0.09, 0.07], 0.8533		0.02 [-0.03, 0.07], 0.4553	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_4_m_pt_ae1pct_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.4410		0.5662		0.9097	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	7/59 (11.9)	0/30 (0.0)	3/50 (6.0)	4/32 (12.5)	10/109 (9.2)	4/62 (6.5)
RR [95%-CI]; p-value	7.24 [0.42, 123.33], 0.1713		0.48 [0.11, 2.01], 0.3143		1.42 [0.47, 4.34], 0.5367	
OR [95%-CI]; p-value	8.08 [0.44, 147.39], 0.0980		0.45 [0.09, 2.14], 0.3042		1.46 [0.44, 4.88], 0.5324	
RD [95%-CI]; p-value	0.10 [0.01, 0.20], 0.0330		-0.07 [-0.20, 0.07], 0.3350		0.03 [-0.05, 0.11], 0.5137	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	8/82 (9.8)	2/42 (4.8)	6/94 (6.4)	3/40 (7.5)	14/176 (8.0)	5/82 (6.1)
RR [95%-CI]; p-value	2.05 [0.46, 9.22], 0.3500		0.85 [0.22, 3.24], 0.8129		1.30 [0.49, 3.50], 0.5975	
OR [95%-CI]; p-value	2.16 [0.44, 10.67], 0.3337		0.84 [0.20, 3.54], 0.8131		1.33 [0.46, 3.83], 0.5949	
RD [95%-CI]; p-value	0.05 [-0.04, 0.14], 0.2818		-0.01 [-0.11, 0.08], 0.8185		0.02 [-0.05, 0.08], 0.5780	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5811		0.8690		0.5721	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	0/59 (0.0)	0/30 (0.0)	1/50 (2.0)	1/32 (3.1)	1/109 (0.9)	1/62 (1.6)
RR [95%-CI]; p-value	NA		0.64 [0.04, 9.87], 0.7492		0.57 [0.04, 8.94], 0.6880	
OR [95%-CI]; p-value	NA		0.63 [0.04, 10.49], 0.7473		0.56 [0.03, 9.19], 0.6843	
RD [95%-CI]; p-value	NA		-0.01 [-0.08, 0.06], 0.7584		-0.01 [-0.04, 0.03], 0.7058	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	2/82 (2.4)	0/42 (0.0)	0/94 (0.0)	0/40 (0.0)	2/176 (1.1)	0/82 (0.0)
RR [95%-CI]; p-value	2.07 [0.10, 44.96], 0.6423		NA		1.88 [0.09, 41.12], 0.6899	
OR [95%-CI]; p-value	2.10 [0.09, 47.62], 0.6339		NA		1.89 [0.08, 42.27], 0.6847	
RD [95%-CI]; p-value	0.01 [-0.03, 0.06], 0.5949		NA		0.01 [-0.02, 0.03], 0.6503	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.3477		0.5363		0.6094	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	7/59 (11.9)	0/30 (0.0)	2/50 (4.0)	3/32 (9.4)	9/109 (8.3)	3/62 (4.8)
RR [95%-CI]; p-value	7.24 [0.42, 123.33], 0.1713		0.43 [0.08, 2.41], 0.3355		1.71 [0.48, 6.07], 0.4091	
OR [95%-CI]; p-value	8.08 [0.44, 147.39], 0.0980		0.40 [0.06, 2.56], 0.3211		1.77 [0.46, 6.80], 0.4002	
RD [95%-CI]; p-value	0.10 [0.01, 0.20], 0.0330		-0.05 [-0.17, 0.06], 0.3583		0.03 [-0.04, 0.11], 0.3673	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	2/42 (4.8)	6/94 (6.4)	3/40 (7.5)	12/176 (6.8)	5/82 (6.1)
RR [95%-CI]; p-value	1.54 [0.32, 7.29], 0.5886		0.85 [0.22, 3.24], 0.8129		1.12 [0.41, 3.07], 0.8284	
OR [95%-CI]; p-value	1.58 [0.30, 8.18], 0.5836		0.84 [0.20, 3.54], 0.8131		1.13 [0.38, 3.31], 0.8280	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5585		-0.01 [-0.11, 0.08], 0.8185		0.01 [-0.06, 0.07], 0.8248	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.9104		0.6351		0.7874	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	0/30 (0.0)	2/50 (4.0)	0/32 (0.0)	4/109 (3.7)	0/62 (0.0)
RR [95%-CI]; p-value	2.07 [0.10, 44.46], 0.6426		2.60 [0.12, 55.86], 0.5415		4.59 [0.25, 85.35], 0.3071	
OR [95%-CI]; p-value	2.11 [0.09, 48.17], 0.6338		2.67 [0.12, 61.06], 0.5239		4.72 [0.25, 90.86], 0.2578	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.5949		0.02 [-0.04, 0.09], 0.4835		0.03 [-0.01, 0.07], 0.1767	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	5/82 (6.1)	1/42 (2.4)	1/94 (1.1)	0/40 (0.0)	6/176 (3.4)	1/82 (1.2)
RR [95%-CI]; p-value	2.56 [0.31, 21.22], 0.3834		0.86 [0.03, 25.18], 0.9311		2.80 [0.34, 22.84], 0.3375	
OR [95%-CI]; p-value	2.66 [0.30, 23.56], 0.3614		0.86 [0.03, 26.16], 0.9311		2.86 [0.34, 24.14], 0.3135	
RD [95%-CI]; p-value	0.04 [-0.03, 0.11], 0.2935		-0.00 [-0.04, 0.04], 0.9330		0.02 [-0.01, 0.06], 0.2309	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7825		0.7742		0.9079	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	5/30 (16.7)	4/50 (8.0)	2/32 (6.3)	10/109 (9.2)	7/62 (11.3)
RR [95%-CI]; p-value	0.61 [0.20, 1.84], 0.3798		1.28 [0.25, 6.59], 0.7678		0.81 [0.33, 2.03], 0.6564	
OR [95%-CI]; p-value	0.57 [0.16, 2.03], 0.3787		1.30 [0.22, 7.57], 0.7666		0.79 [0.29, 2.20], 0.6566	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4085		0.02 [-0.10, 0.13], 0.7608		-0.02 [-0.12, 0.07], 0.6645	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	6/82 (7.3)	4/42 (9.5)	9/94 (9.6)	4/40 (10.0)	15/176 (8.5)	8/82 (9.8)
RR [95%-CI]; p-value	0.77 [0.23, 2.57], 0.6692		0.96 [0.31, 2.93], 0.9392		0.87 [0.39, 1.98], 0.7458	
OR [95%-CI]; p-value	0.75 [0.20, 2.82], 0.6693		0.95 [0.28, 3.29], 0.9393		0.86 [0.35, 2.12], 0.7462	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.08], 0.6809		-0.00 [-0.11, 0.11], 0.9398		-0.01 [-0.09, 0.06], 0.7515	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5811		0.5724		0.9141	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	0/59 (0.0)	0/30 (0.0)	2/50 (4.0)	0/32 (0.0)	2/109 (1.8)	0/62 (0.0)
RR [95%-CI]; p-value	NA		2.60 [0.12, 55.86], 0.5415		2.29 [0.11, 50.07], 0.5977	
OR [95%-CI]; p-value	NA		2.67 [0.12, 61.06], 0.5239		2.32 [0.10, 52.21], 0.5863	
RD [95%-CI]; p-value	NA		0.02 [-0.04, 0.09], 0.4835		0.01 [-0.02, 0.04], 0.5449	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	2/82 (2.4)	0/42 (0.0)	2/94 (2.1)	1/40 (2.5)	4/176 (2.3)	1/82 (1.2)
RR [95%-CI]; p-value	2.07 [0.10, 44.96], 0.6423		0.85 [0.08, 9.12], 0.8940		1.86 [0.21, 16.41], 0.5749	
OR [95%-CI]; p-value	2.10 [0.09, 47.62], 0.6339		0.85 [0.07, 9.63], 0.8939		1.88 [0.21, 17.12], 0.5677	
RD [95%-CI]; p-value	0.01 [-0.03, 0.06], 0.5949		-0.00 [-0.06, 0.05], 0.8972		0.01 [-0.02, 0.04], 0.5239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.8429		0.8119		0.8394	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	6/59 (10.2)	5/30 (16.7)	3/50 (6.0)	2/32 (6.3)	9/109 (8.3)	7/62 (11.3)
RR [95%-CI]; p-value	0.61 [0.20, 1.84], 0.3798		0.96 [0.17, 5.43], 0.9632		0.73 [0.29, 1.87], 0.5129	
OR [95%-CI]; p-value	0.57 [0.16, 2.03], 0.3787		0.96 [0.15, 6.07], 0.9632		0.71 [0.25, 2.00], 0.5126	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4085		-0.00 [-0.11, 0.10], 0.9633		-0.03 [-0.12, 0.06], 0.5280	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	4/82 (4.9)	4/42 (9.5)	7/94 (7.4)	4/40 (10.0)	11/176 (6.3)	8/82 (9.8)
RR [95%-CI]; p-value	0.51 [0.13, 1.95], 0.3260		0.74 [0.23, 2.40], 0.6218		0.64 [0.27, 1.53], 0.3170	
OR [95%-CI]; p-value	0.49 [0.12, 2.05], 0.3190		0.72 [0.20, 2.63], 0.6222		0.62 [0.24, 1.60], 0.3154	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3638		-0.03 [-0.13, 0.08], 0.6402		-0.04 [-0.11, 0.04], 0.3499	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.7.s1
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8514		0.8949		0.9770	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	2/59 (3.4)	0/30 (0.0)	1/50 (2.0)	0/32 (0.0)	3/109 (2.8)	0/62 (0.0)
RR [95%-CI]; p-value	2.07 [0.10, 44.46], 0.6426		1.30 [0.04, 37.65], 0.8786		3.44 [0.18, 67.58], 0.4161	
OR [95%-CI]; p-value	2.11 [0.09, 48.17], 0.6338		1.31 [0.04, 40.08], 0.8782		3.51 [0.17, 71.22], 0.3842	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.5949		0.00 [-0.05, 0.06], 0.8748		0.02 [-0.02, 0.06], 0.3118	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	3/82 (3.7)	0/42 (0.0)	4/94 (4.3)	1/40 (2.5)	7/176 (4.0)	1/82 (1.2)
RR [95%-CI]; p-value	3.11 [0.16, 60.67], 0.4542		1.70 [0.20, 14.76], 0.6293		3.26 [0.41, 26.08], 0.2650	
OR [95%-CI]; p-value	3.19 [0.16, 65.18], 0.4269		1.73 [0.19, 16.01], 0.6237		3.36 [0.41, 27.73], 0.2341	
RD [95%-CI]; p-value	0.02 [-0.03, 0.08], 0.3493		0.02 [-0.05, 0.08], 0.5867		0.03 [-0.01, 0.06], 0.1483	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_7_m_pt_smq_age.sas using SAS 9.4

Table 12.4.4.1.6.s1
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.1876		0.3370		0.1404	
1.Age < 65 yrs	N1=59	N1=30	N1=50	N1=32	N1=109	N1=62
n/N1 (%)	9/59 (15.3)	10/30 (33.3)	11/50 (22.0)	6/32 (18.8)	20/109 (18.3)	16/62 (25.8)
RR [95%-CI]; p-value	0.46 [0.21, 1.00], 0.0513		1.17 [0.48, 2.86], 0.7249		0.71 [0.40, 1.27], 0.2481	
OR [95%-CI]; p-value	0.36 [0.13, 1.02], 0.0491		1.22 [0.40, 3.71], 0.7232		0.65 [0.31, 1.36], 0.2501	
RD [95%-CI]; p-value	-0.18 [-0.37, 0.01], 0.0650		0.03 [-0.14, 0.21], 0.7195		-0.07 [-0.21, 0.06], 0.2643	
2.Age ≥ 65 yrs	N2=82	N2=42	N2=94	N2=40	N2=176	N2=82
n/N2 (%)	15/82 (18.3)	8/42 (19.0)	17/94 (18.1)	3/40 (7.5)	32/176 (18.2)	11/82 (13.4)
RR [95%-CI]; p-value	0.96 [0.44, 2.08], 0.9184		2.41 [0.75, 7.77], 0.1404		1.36 [0.72, 2.55], 0.3464	
OR [95%-CI]; p-value	0.95 [0.37, 2.47], 0.9185		2.72 [0.75, 9.88], 0.1156		1.43 [0.68, 3.01], 0.3387	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.14], 0.9189		0.11 [-0.01, 0.22], 0.0658		0.05 [-0.05, 0.14], 0.3161	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age/T12_4_4_1_6_m_pt_adr_age.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.8203		0.0333		0.0650	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	56/71 (78.9)	28/33 (84.8)	50/71 (70.4)	21/39 (53.8)	106/142 (74.6)	49/72 (68.1)
RR [95%-CI]; p-value	0.93 [0.77, 1.12], 0.4461		1.31 [0.94, 1.81], 0.1081		1.10 [0.91, 1.32], 0.3274	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4718		2.04 [0.91, 4.59], 0.0821		1.38 [0.74, 2.58], 0.3079	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4495		0.17 [-0.02, 0.35], 0.0857		0.07 [-0.06, 0.20], 0.3177	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	45/70 (64.3)	28/39 (71.8)	41/73 (56.2)	23/33 (69.7)	86/143 (60.1)	51/72 (70.8)
RR [95%-CI]; p-value	0.90 [0.69, 1.16], 0.4104		0.81 [0.60, 1.09], 0.1623		0.85 [0.70, 1.04], 0.1078	
OR [95%-CI]; p-value	0.71 [0.30, 1.66], 0.4243		0.56 [0.23, 1.34], 0.1872		0.62 [0.34, 1.14], 0.1238	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.11], 0.4146		-0.14 [-0.33, 0.06], 0.1710		-0.11 [-0.24, 0.03], 0.1127	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.3985		0.2945		0.9535	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	7/33 (21.2)	10/71 (14.1)	0/39 (0.0)	19/142 (13.4)	7/72 (9.7)
RR [95%-CI]; p-value	0.60 [0.24, 1.47], 0.2607		11.13 [0.67, 185.46], 0.0933		1.38 [0.61, 3.12], 0.4446	
OR [95%-CI]; p-value	0.54 [0.18, 1.60], 0.2615		12.79 [0.73, 225.19], 0.0277		1.43 [0.57, 3.59], 0.4390	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.07], 0.2942		0.13 [0.04, 0.22], 0.0044		0.04 [-0.05, 0.13], 0.4174	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	8/70 (11.4)	4/39 (10.3)	9/73 (12.3)	2/33 (6.1)	17/143 (11.9)	6/72 (8.3)
RR [95%-CI]; p-value	1.11 [0.36, 3.47], 0.8517		2.03 [0.46, 8.90], 0.3457		1.43 [0.59, 3.46], 0.4322	
OR [95%-CI]; p-value	1.13 [0.32, 4.02], 0.8513		2.18 [0.44, 10.70], 0.3272		1.48 [0.56, 3.94], 0.4261	
RD [95%-CI]; p-value	0.01 [-0.11, 0.13], 0.8493		0.06 [-0.05, 0.17], 0.2683		0.04 [-0.05, 0.12], 0.4012	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.9496		0.6109		0.7725	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	2/33 (6.1)	5/71 (7.0)	3/39 (7.7)	12/142 (8.5)	5/72 (6.9)
RR [95%-CI]; p-value	1.63 [0.36, 7.41], 0.5294		0.92 [0.23, 3.63], 0.9000		1.22 [0.45, 3.32], 0.7016	
OR [95%-CI]; p-value	1.70 [0.33, 8.64], 0.5214		0.91 [0.21, 4.03], 0.9001		1.24 [0.42, 3.66], 0.7002	
RD [95%-CI]; p-value	0.04 [-0.07, 0.14], 0.4863		-0.01 [-0.11, 0.10], 0.9012		0.02 [-0.06, 0.09], 0.6917	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	4/39 (10.3)	5/73 (6.8)	4/33 (12.1)	16/143 (11.2)	8/72 (11.1)
RR [95%-CI]; p-value	1.53 [0.52, 4.49], 0.4367		0.57 [0.16, 1.97], 0.3703		1.01 [0.45, 2.24], 0.9864	
OR [95%-CI]; p-value	1.63 [0.48, 5.52], 0.4278		0.53 [0.13, 2.13], 0.3673		1.01 [0.41, 2.48], 0.9864	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4026		-0.05 [-0.18, 0.07], 0.4104		0.00 [-0.09, 0.09], 0.9864	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.0763		0.7921		0.2207	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	15/71 (21.1)	2/33 (6.1)	8/71 (11.3)	5/39 (12.8)	23/142 (16.2)	7/72 (9.7)
RR [95%-CI]; p-value	3.49 [0.85, 14.37], 0.0840		0.88 [0.31, 2.50], 0.8090		1.67 [0.75, 3.70], 0.2095	
OR [95%-CI]; p-value	4.15 [0.89, 19.35], 0.0531		0.86 [0.26, 2.85], 0.8093		1.79 [0.73, 4.41], 0.1974	
RD [95%-CI]; p-value	0.15 [0.03, 0.28], 0.0182		-0.02 [-0.14, 0.11], 0.8122		0.06 [-0.03, 0.16], 0.1650	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	15/70 (21.4)	10/39 (25.6)	14/73 (19.2)	6/33 (18.2)	29/143 (20.3)	16/72 (22.2)
RR [95%-CI]; p-value	0.84 [0.42, 1.68], 0.6142		1.05 [0.44, 2.50], 0.9036		0.91 [0.53, 1.57], 0.7402	
OR [95%-CI]; p-value	0.79 [0.32, 1.98], 0.6161		1.07 [0.37, 3.08], 0.9034		0.89 [0.45, 1.77], 0.7411	
RD [95%-CI]; p-value	-0.04 [-0.21, 0.13], 0.6218		0.01 [-0.15, 0.17], 0.9026		-0.02 [-0.14, 0.10], 0.7437	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.0509		0.2467		0.4614	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	4/33 (12.1)	8/71 (11.3)	1/39 (2.6)	13/142 (9.2)	5/72 (6.9)
RR [95%-CI]; p-value	0.58 [0.17, 2.02], 0.3939		4.39 [0.57, 33.86], 0.1553		1.32 [0.49, 3.55], 0.5849	
OR [95%-CI]; p-value	0.55 [0.14, 2.19], 0.3912		4.83 [0.58, 40.10], 0.1111		1.35 [0.46, 3.95], 0.5820	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4305		0.09 [-0.00, 0.18], 0.0545		0.02 [-0.05, 0.10], 0.5660	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	1/39 (2.6)	7/73 (9.6)	3/33 (9.1)	18/143 (12.6)	4/72 (5.6)
RR [95%-CI]; p-value	6.13 [0.82, 45.71], 0.0770		1.05 [0.29, 3.83], 0.9353		2.27 [0.80, 6.45], 0.1253	
OR [95%-CI]; p-value	7.08 [0.88, 57.13], 0.0355		1.06 [0.26, 4.39], 0.9352		2.45 [0.80, 7.52], 0.1084	
RD [95%-CI]; p-value	0.13 [0.03, 0.23], 0.0090		0.00 [-0.11, 0.12], 0.9347		0.07 [-0.01, 0.15], 0.0693	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.4258		0.4057		0.9946	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	2/71 (2.8)	1/33 (3.0)	4/71 (5.6)	1/39 (2.6)	6/142 (4.2)	2/72 (2.8)
RR [95%-CI]; p-value	0.93 [0.09, 9.89], 0.9517		2.20 [0.25, 18.98], 0.4743		1.52 [0.31, 7.35], 0.6017	
OR [95%-CI]; p-value	0.93 [0.08, 10.61], 0.9517		2.27 [0.24, 21.04], 0.4597		1.54 [0.30, 7.85], 0.5979	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.07], 0.9524		0.03 [-0.04, 0.10], 0.4102		0.01 [-0.04, 0.06], 0.5731	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	6/70 (8.6)	1/39 (2.6)	3/73 (4.1)	2/33 (6.1)	9/143 (6.3)	3/72 (4.2)
RR [95%-CI]; p-value	3.34 [0.42, 26.77], 0.2556		0.68 [0.12, 3.87], 0.6619		1.51 [0.42, 5.41], 0.5263	
OR [95%-CI]; p-value	3.56 [0.41, 30.73], 0.2201		0.66 [0.11, 4.18], 0.6609		1.54 [0.41, 5.89], 0.5214	
RD [95%-CI]; p-value	0.06 [-0.02, 0.14], 0.1522		-0.02 [-0.11, 0.07], 0.6818		0.02 [-0.04, 0.08], 0.4940	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.4521		0.9213		0.6767	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	1/71 (1.4)	1/33 (3.0)	1/71 (1.4)	0/39 (0.0)	2/142 (1.4)	1/72 (1.4)
RR [95%-CI]; p-value	0.46 [0.03, 7.20], 0.5838		1.11 [0.04, 32.43], 0.9505		1.01 [0.09, 11.00], 0.9908	
OR [95%-CI]; p-value	0.46 [0.03, 7.54], 0.5751		1.11 [0.04, 33.97], 0.9505		1.01 [0.09, 11.38], 0.9908	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.05], 0.6226		0.00 [-0.04, 0.05], 0.9497		0.00 [-0.03, 0.03], 0.9908	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	2/70 (2.9)	0/39 (0.0)	2/73 (2.7)	1/33 (3.0)	4/143 (2.8)	1/72 (1.4)
RR [95%-CI]; p-value	2.26 [0.10, 48.83], 0.6038		0.90 [0.08, 9.62], 0.9334		2.01 [0.23, 17.69], 0.5277	
OR [95%-CI]; p-value	2.29 [0.10, 52.16], 0.5924		0.90 [0.08, 10.31], 0.9334		2.04 [0.22, 18.62], 0.5179	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5512		-0.00 [-0.07, 0.07], 0.9346		0.01 [-0.02, 0.05], 0.4702	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.1465		0.1536		0.0366	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	51/71 (71.8)	25/33 (75.8)	38/71 (53.5)	17/39 (43.6)	89/142 (62.7)	42/72 (58.3)
RR [95%-CI]; p-value	0.95 [0.74, 1.21], 0.6662		1.23 [0.81, 1.86], 0.3355		1.07 [0.85, 1.36], 0.5456	
OR [95%-CI]; p-value	0.82 [0.32, 2.11], 0.6744		1.49 [0.68, 3.27], 0.3190		1.20 [0.67, 2.14], 0.5379	
RD [95%-CI]; p-value	-0.04 [-0.22, 0.14], 0.6686		0.10 [-0.09, 0.29], 0.3160		0.04 [-0.10, 0.18], 0.5401	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	31/70 (44.3)	25/39 (64.1)	32/73 (43.8)	18/33 (54.5)	63/143 (44.1)	43/72 (59.7)
RR [95%-CI]; p-value	0.69 [0.49, 0.98], 0.0397		0.80 [0.54, 1.21], 0.2907		0.74 [0.57, 0.96], 0.0243	
OR [95%-CI]; p-value	0.45 [0.20, 1.00], 0.0472		0.65 [0.28, 1.49], 0.3064		0.53 [0.30, 0.94], 0.0301	
RD [95%-CI]; p-value	-0.20 [-0.39, -0.01], 0.0412		-0.11 [-0.31, 0.10], 0.3047		-0.16 [-0.30, -0.02], 0.0277	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.3233		0.0186		0.0118	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	24/71 (33.8)	10/33 (30.3)	28/71 (39.4)	6/39 (15.4)	52/142 (36.6)	16/72 (22.2)
RR [95%-CI]; p-value	1.12 [0.61, 2.06], 0.7260		2.56 [1.16, 5.65], 0.0196		1.65 [1.02, 2.67], 0.0428	
OR [95%-CI]; p-value	1.17 [0.48, 2.86], 0.7232		3.58 [1.33, 9.65], 0.0090		2.02 [1.05, 3.88], 0.0326	
RD [95%-CI]; p-value	0.03 [-0.16, 0.23], 0.7203		0.24 [0.08, 0.40], 0.0033		0.14 [0.02, 0.27], 0.0234	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	26/70 (37.1)	19/39 (48.7)	21/73 (28.8)	12/33 (36.4)	47/143 (32.9)	31/72 (43.1)
RR [95%-CI]; p-value	0.76 [0.49, 1.19], 0.2304		0.79 [0.44, 1.41], 0.4268		0.76 [0.54, 1.09], 0.1351	
OR [95%-CI]; p-value	0.62 [0.28, 1.38], 0.2394		0.71 [0.30, 1.69], 0.4342		0.65 [0.36, 1.16], 0.1425	
RD [95%-CI]; p-value	-0.12 [-0.31, 0.08], 0.2409		-0.08 [-0.27, 0.12], 0.4433		-0.10 [-0.24, 0.04], 0.1475	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.3.1.s2
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.9496		0.6109		0.7725	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	2/33 (6.1)	5/71 (7.0)	3/39 (7.7)	12/142 (8.5)	5/72 (6.9)
RR [95%-CI]; p-value	1.63 [0.36, 7.41], 0.5294		0.92 [0.23, 3.63], 0.9000		1.22 [0.45, 3.32], 0.7016	
OR [95%-CI]; p-value	1.70 [0.33, 8.64], 0.5214		0.91 [0.21, 4.03], 0.9001		1.24 [0.42, 3.66], 0.7002	
RD [95%-CI]; p-value	0.04 [-0.07, 0.14], 0.4863		-0.01 [-0.11, 0.10], 0.9012		0.02 [-0.06, 0.09], 0.6917	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	4/39 (10.3)	5/73 (6.8)	4/33 (12.1)	16/143 (11.2)	8/72 (11.1)
RR [95%-CI]; p-value	1.53 [0.52, 4.49], 0.4367		0.57 [0.16, 1.97], 0.3703		1.01 [0.45, 2.24], 0.9864	
OR [95%-CI]; p-value	1.63 [0.48, 5.52], 0.4278		0.53 [0.13, 2.13], 0.3673		1.01 [0.41, 2.48], 0.9864	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4026		-0.05 [-0.18, 0.07], 0.4104		0.00 [-0.09, 0.09], 0.9864	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_3_1_m_sf_ttl_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.5997		0.9912		0.5273	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	2/33 (6.1)	5/71 (7.0)	2/39 (5.1)	9/142 (6.3)	4/72 (5.6)
RR [95%-CI]; p-value	0.93 [0.18, 4.82], 0.9307		1.37 [0.28, 6.75], 0.6963		1.14 [0.36, 3.58], 0.8213	
OR [95%-CI]; p-value	0.93 [0.16, 5.32], 0.9308		1.40 [0.26, 7.58], 0.6940		1.15 [0.34, 3.87], 0.8209	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9316		0.02 [-0.07, 0.11], 0.6811		0.01 [-0.06, 0.07], 0.8173	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	6/73 (8.2)	2/33 (6.1)	13/143 (9.1)	9/72 (12.5)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		1.36 [0.29, 6.37], 0.6994		0.73 [0.33, 1.62], 0.4360	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		1.39 [0.26, 7.27], 0.6969		0.70 [0.28, 1.72], 0.4363	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		0.02 [-0.08, 0.12], 0.6811		-0.03 [-0.12, 0.06], 0.4566	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8351		0.3282		0.3739	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	16/71 (22.5)	10/33 (30.3)	15/71 (21.1)	3/39 (7.7)	31/142 (21.8)	13/72 (18.1)
RR [95%-CI]; p-value	0.74 [0.38, 1.46], 0.3888		2.75 [0.85, 8.91], 0.0923		1.21 [0.68, 2.16], 0.5227	
OR [95%-CI]; p-value	0.67 [0.26, 1.69], 0.3945		3.21 [0.87, 11.89], 0.0685		1.27 [0.62, 2.61], 0.5185	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.11], 0.4092		0.13 [0.01, 0.26], 0.0374		0.04 [-0.07, 0.15], 0.5082	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	12/70 (17.1)	10/39 (25.6)	11/73 (15.1)	4/33 (12.1)	23/143 (16.1)	14/72 (19.4)
RR [95%-CI]; p-value	0.67 [0.32, 1.40], 0.2877		1.24 [0.43, 3.62], 0.6896		0.83 [0.45, 1.51], 0.5361	
OR [95%-CI]; p-value	0.60 [0.23, 1.55], 0.2893		1.29 [0.38, 4.38], 0.6869		0.79 [0.38, 1.66], 0.5378	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.08], 0.3069		0.03 [-0.11, 0.17], 0.6762		-0.03 [-0.14, 0.08], 0.5474	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9269		0.2973		0.4477	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	7/33 (21.2)	7/71 (9.9)	3/39 (7.7)	17/142 (12.0)	10/72 (13.9)
RR [95%-CI]; p-value	0.66 [0.28, 1.59], 0.3580		1.28 [0.35, 4.68], 0.7072		0.86 [0.42, 1.78], 0.6892	
OR [95%-CI]; p-value	0.61 [0.21, 1.77], 0.3603		1.31 [0.32, 5.39], 0.7053		0.84 [0.36, 1.95], 0.6898	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.09], 0.3863		0.02 [-0.09, 0.13], 0.6959		-0.02 [-0.12, 0.08], 0.6958	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	8/39 (20.5)	10/73 (13.7)	8/33 (24.2)	19/143 (13.3)	16/72 (22.2)
RR [95%-CI]; p-value	0.63 [0.26, 1.49], 0.2916		0.57 [0.25, 1.30], 0.1797		0.60 [0.33, 1.09], 0.0939	
OR [95%-CI]; p-value	0.57 [0.20, 1.63], 0.2910		0.50 [0.18, 1.40], 0.1807		0.54 [0.26, 1.12], 0.0939	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3140		-0.11 [-0.27, 0.06], 0.2135		-0.09 [-0.20, 0.02], 0.1146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.3270		0.6637		0.2794	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	25/71 (35.2)	10/33 (30.3)	21/71 (29.6)	10/39 (25.6)	46/142 (32.4)	20/72 (27.8)
RR [95%-CI]; p-value	1.16 [0.63, 2.13], 0.6273		1.15 [0.61, 2.20], 0.6637		1.17 [0.75, 1.81], 0.4952	
OR [95%-CI]; p-value	1.25 [0.51, 3.04], 0.6220		1.22 [0.50, 2.94], 0.6607		1.25 [0.67, 2.33], 0.4896	
RD [95%-CI]; p-value	0.05 [-0.14, 0.24], 0.6167		0.04 [-0.13, 0.21], 0.6563		0.05 [-0.08, 0.18], 0.4829	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	13/70 (18.6)	10/39 (25.6)	12/73 (16.4)	6/33 (18.2)	25/143 (17.5)	16/72 (22.2)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3835		0.90 [0.37, 2.20], 0.8242		0.79 [0.45, 1.38], 0.4011	
OR [95%-CI]; p-value	0.66 [0.26, 1.69], 0.3859		0.89 [0.30, 2.61], 0.8248		0.74 [0.37, 1.50], 0.4038	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.09], 0.3998		-0.02 [-0.17, 0.14], 0.8273		-0.05 [-0.16, 0.07], 0.4169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8173		0.4316		0.5270	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	4/71 (5.6)	2/39 (5.1)	14/142 (9.9)	5/72 (6.9)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.21, 5.73], 0.9112		1.42 [0.53, 3.79], 0.4838	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.10 [0.19, 6.32], 0.9111		1.47 [0.51, 4.24], 0.4788	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.08, 0.09], 0.9099		0.03 [-0.05, 0.11], 0.4552	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	2/39 (5.1)	7/73 (9.6)	1/33 (3.0)	14/143 (9.8)	3/72 (4.2)
RR [95%-CI]; p-value	1.95 [0.43, 8.93], 0.3898		3.16 [0.41, 24.69], 0.2718		2.35 [0.70, 7.91], 0.1680	
OR [95%-CI]; p-value	2.06 [0.41, 10.42], 0.3757		3.39 [0.40, 28.77], 0.2365		2.50 [0.69, 8.98], 0.1493	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3331		0.07 [-0.02, 0.15], 0.1502		0.06 [-0.01, 0.12], 0.1005	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1992		0.8266		0.2485	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	6/71 (8.5)	3/39 (7.7)	16/142 (11.3)	6/72 (8.3)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.29, 4.15], 0.8898		1.35 [0.55, 3.31], 0.5086	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.11 [0.26, 4.70], 0.8896		1.40 [0.52, 3.74], 0.5043	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.10, 0.11], 0.8882		0.03 [-0.05, 0.11], 0.4849	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	8/73 (11.0)	4/33 (12.1)	15/143 (10.5)	11/72 (15.3)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		0.90 [0.29, 2.79], 0.8609		0.69 [0.33, 1.42], 0.3091	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		0.89 [0.25, 3.20], 0.8612		0.65 [0.28, 1.50], 0.3095	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		-0.01 [-0.14, 0.12], 0.8634		-0.05 [-0.14, 0.05], 0.3338	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0323		0.2866		0.3081	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	17/71 (23.9)	6/33 (18.2)	10/71 (14.1)	8/39 (20.5)	27/142 (19.0)	14/72 (19.4)
RR [95%-CI]; p-value	1.32 [0.57, 3.03], 0.5177		0.69 [0.30, 1.60], 0.3824		0.98 [0.55, 1.75], 0.9397	
OR [95%-CI]; p-value	1.42 [0.50, 4.00], 0.5099		0.64 [0.23, 1.77], 0.3833		0.97 [0.47, 2.00], 0.9397	
RD [95%-CI]; p-value	0.06 [-0.11, 0.22], 0.4933		-0.06 [-0.21, 0.09], 0.4021		-0.00 [-0.12, 0.11], 0.9399	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	15/39 (38.5)	15/73 (20.5)	5/33 (15.2)	26/143 (18.2)	20/72 (27.8)
RR [95%-CI]; p-value	0.41 [0.21, 0.80], 0.0091		1.36 [0.54, 3.42], 0.5185		0.65 [0.39, 1.09], 0.1030	
OR [95%-CI]; p-value	0.30 [0.12, 0.74], 0.0076		1.45 [0.48, 4.39], 0.5108		0.58 [0.30, 1.13], 0.1054	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.05], 0.0108		0.05 [-0.10, 0.21], 0.4907		-0.10 [-0.22, 0.03], 0.1208	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5879		0.1012		0.4410	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	13/71 (18.3)	13/33 (39.4)	14/71 (19.7)	6/39 (15.4)	27/142 (19.0)	19/72 (26.4)
RR [95%-CI]; p-value	0.46 [0.24, 0.89], 0.0206		1.28 [0.54, 3.07], 0.5774		0.72 [0.43, 1.20], 0.2112	
OR [95%-CI]; p-value	0.34 [0.14, 0.87], 0.0208		1.35 [0.47, 3.85], 0.5729		0.65 [0.33, 1.28], 0.2146	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.02], 0.0292		0.04 [-0.10, 0.19], 0.5614		-0.07 [-0.19, 0.05], 0.2305	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	10/39 (25.6)	8/73 (11.0)	8/33 (24.2)	19/143 (13.3)	18/72 (25.0)
RR [95%-CI]; p-value	0.61 [0.29, 1.31], 0.2076		0.45 [0.19, 1.10], 0.0802		0.53 [0.30, 0.95], 0.0324	
OR [95%-CI]; p-value	0.54 [0.21, 1.42], 0.2078		0.38 [0.13, 1.14], 0.0769		0.46 [0.22, 0.94], 0.0318	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2280		-0.13 [-0.30, 0.03], 0.1098		-0.12 [-0.23, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9989		0.6150		0.7564	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	7/33 (21.2)	11/71 (15.5)	4/39 (10.3)	18/142 (12.7)	11/72 (15.3)
RR [95%-CI]; p-value	0.46 [0.18, 1.22], 0.1188		1.51 [0.52, 4.43], 0.4523		0.83 [0.41, 1.66], 0.5983	
OR [95%-CI]; p-value	0.41 [0.13, 1.27], 0.1144		1.60 [0.47, 5.42], 0.4439		0.80 [0.36, 1.81], 0.5993	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.04], 0.1531		0.05 [-0.07, 0.18], 0.4193		-0.03 [-0.13, 0.07], 0.6083	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	9/73 (12.3)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		1.02 [0.34, 3.07], 0.9759		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		1.02 [0.29, 3.58], 0.9759		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		0.00 [-0.13, 0.14], 0.9759		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7918		0.1249		0.3349	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	6/33 (18.2)	12/71 (16.9)	3/39 (7.7)	21/142 (14.8)	9/72 (12.5)
RR [95%-CI]; p-value	0.70 [0.27, 1.80], 0.4553		2.20 [0.66, 7.32], 0.1998		1.18 [0.57, 2.45], 0.6506	
OR [95%-CI]; p-value	0.65 [0.21, 2.02], 0.4570		2.44 [0.64, 9.24], 0.1782		1.21 [0.53, 2.81], 0.6486	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4797		0.09 [-0.03, 0.21], 0.1351		0.02 [-0.07, 0.12], 0.6408	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	6/39 (15.4)	5/73 (6.8)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.84 [0.32, 2.17], 0.7129		0.57 [0.16, 1.97], 0.3703		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.81 [0.27, 2.48], 0.7135		0.53 [0.13, 2.13], 0.3673		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7191		-0.05 [-0.18, 0.07], 0.4104		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7563		0.0951		0.0960	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	3/33 (9.1)	7/71 (9.9)	0/39 (0.0)	11/142 (7.7)	3/72 (4.2)
RR [95%-CI]; p-value	0.62 [0.15, 2.61], 0.5145		7.79 [0.45, 133.66], 0.1570		1.86 [0.54, 6.45], 0.3288	
OR [95%-CI]; p-value	0.60 [0.13, 2.83], 0.5125		8.53 [0.47, 154.52], 0.0852		1.93 [0.52, 7.15], 0.3170	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.08], 0.5444		0.09 [0.01, 0.16], 0.0300		0.04 [-0.03, 0.10], 0.2711	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	8/73 (11.0)	6/33 (18.2)	13/143 (9.1)	12/72 (16.7)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		0.60 [0.23, 1.60], 0.3090		0.55 [0.26, 1.13], 0.1045	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		0.55 [0.18, 1.75], 0.3091		0.50 [0.22, 1.16], 0.1020	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		-0.07 [-0.22, 0.08], 0.3448		-0.08 [-0.17, 0.02], 0.1303	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.1.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7336		0.4179		0.7370	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	8/71 (11.3)	5/33 (15.2)	3/71 (4.2)	1/39 (2.6)	11/142 (7.7)	6/72 (8.3)
RR [95%-CI]; p-value	0.74 [0.26, 2.10], 0.5761		1.65 [0.18, 15.31], 0.6605		0.93 [0.36, 2.41], 0.8807	
OR [95%-CI]; p-value	0.71 [0.21, 2.37], 0.5772		1.68 [0.17, 16.68], 0.6561		0.92 [0.33, 2.61], 0.8808	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.10], 0.5938		0.02 [-0.05, 0.08], 0.6330		-0.01 [-0.08, 0.07], 0.8820	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	4/39 (10.3)	8/73 (11.0)	6/33 (18.2)	15/143 (10.5)	10/72 (13.9)
RR [95%-CI]; p-value	0.98 [0.30, 3.12], 0.9660		0.60 [0.23, 1.60], 0.3090		0.76 [0.36, 1.60], 0.4622	
OR [95%-CI]; p-value	0.97 [0.27, 3.55], 0.9660		0.55 [0.18, 1.75], 0.3091		0.73 [0.31, 1.71], 0.4630	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9661		-0.07 [-0.22, 0.08], 0.3448		-0.03 [-0.13, 0.06], 0.4801	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_1_m_soc_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.3.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3715		0.9283		0.4007	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	3/71 (4.2)	8/33 (24.2)	3/71 (4.2)	0/39 (0.0)	6/142 (4.2)	8/72 (11.1)
RR [95%-CI]; p-value	0.17 [0.05, 0.62], 0.0066		3.34 [0.17, 64.97], 0.4261		0.38 [0.14, 1.05], 0.0631	
OR [95%-CI]; p-value	0.14 [0.03, 0.56], 0.0020		3.44 [0.17, 70.49], 0.3946		0.35 [0.12, 1.06], 0.0543	
RD [95%-CI]; p-value	-0.20 [-0.35, -0.05], 0.0106		0.03 [-0.03, 0.09], 0.3202		-0.07 [-0.15, 0.01], 0.0907	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	4/39 (10.3)	3/73 (4.1)	0/33 (0.0)	6/143 (4.2)	4/72 (5.6)
RR [95%-CI]; p-value	0.42 [0.10, 1.77], 0.2365		2.75 [0.14, 53.45], 0.5033		0.76 [0.22, 2.59], 0.6554	
OR [95%-CI]; p-value	0.39 [0.08, 1.85], 0.2229		2.83 [0.14, 58.10], 0.4818		0.74 [0.20, 2.73], 0.6550	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.2713		0.03 [-0.04, 0.09], 0.4029		-0.01 [-0.08, 0.05], 0.6687	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_3_m_pt_ae10pct_sex.sas using SAS 9.4

Table 12.4.4.1.3.s2
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0996		0.4314		0.3278	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	6/71 (8.5)	4/33 (12.1)	4/71 (5.6)	3/39 (7.7)	10/142 (7.0)	7/72 (9.7)
RR [95%-CI]; p-value	0.70 [0.21, 2.31], 0.5544		0.73 [0.17, 3.11], 0.6727		0.72 [0.29, 1.82], 0.4936	
OR [95%-CI]; p-value	0.67 [0.18, 2.55], 0.5545		0.72 [0.15, 3.38], 0.6722		0.70 [0.26, 1.93], 0.4933	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5764		-0.02 [-0.12, 0.08], 0.6847		-0.03 [-0.11, 0.05], 0.5132	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	1/70 (1.4)	6/39 (15.4)	3/73 (4.1)	0/33 (0.0)	4/143 (2.8)	6/72 (8.3)
RR [95%-CI]; p-value	0.09 [0.01, 0.74], 0.0252		2.75 [0.14, 53.45], 0.5033		0.34 [0.10, 1.15], 0.0827	
OR [95%-CI]; p-value	0.08 [0.01, 0.69], 0.0044		2.83 [0.14, 58.10], 0.4818		0.32 [0.09, 1.16], 0.0689	
RD [95%-CI]; p-value	-0.14 [-0.26, -0.02], 0.0190		0.03 [-0.04, 0.09], 0.4029		-0.06 [-0.12, 0.01], 0.1175	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_3_m_pt_ae10pct_sex.sas using SAS 9.4

Table 12.4.8.1.1.s2
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9994		0.2484		0.4182	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	3/71 (4.2)	1/33 (3.0)	1/71 (1.4)	2/39 (5.1)	4/142 (2.8)	3/72 (4.2)
RR [95%-CI]; p-value	1.39 [0.15, 12.91], 0.7697		0.27 [0.03, 2.93], 0.2849		0.68 [0.16, 2.94], 0.6017	
OR [95%-CI]; p-value	1.41 [0.14, 14.11], 0.7680		0.26 [0.02, 3.01], 0.2519		0.67 [0.15, 3.06], 0.5999	
RD [95%-CI]; p-value	0.01 [-0.06, 0.09], 0.7545		-0.04 [-0.11, 0.04], 0.3275		-0.01 [-0.07, 0.04], 0.6215	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	2/39 (5.1)	4/73 (5.5)	1/33 (3.0)	9/143 (6.3)	3/72 (4.2)
RR [95%-CI]; p-value	1.39 [0.28, 6.85], 0.6834		1.81 [0.21, 15.56], 0.5896		1.51 [0.42, 5.41], 0.5263	
OR [95%-CI]; p-value	1.42 [0.26, 7.70], 0.6809		1.86 [0.20, 17.27], 0.5818		1.54 [0.41, 5.89], 0.5214	
RD [95%-CI]; p-value	0.02 [-0.07, 0.11], 0.6672		0.02 [-0.05, 0.10], 0.5403		0.02 [-0.04, 0.08], 0.4940	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_8_1_1_m_soc_sae5pct_sex.sas using SAS 9.4

Table 12.4.8.1.2.s2
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_8_1_2_m_pt_sae5pct_sex.sas using SAS 9.4

Table 12.4.5.1.1.s2
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_5_1_1_m_soc_aeg35pct_sex.sas using SAS 9.4

Table 12.4.5.1.2.s2
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_5_1_2_m_pt_aeg35pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.5997		0.9912		0.5273	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	2/33 (6.1)	5/71 (7.0)	2/39 (5.1)	9/142 (6.3)	4/72 (5.6)
RR [95%-CI]; p-value	0.93 [0.18, 4.82], 0.9307		1.37 [0.28, 6.75], 0.6963		1.14 [0.36, 3.58], 0.8213	
OR [95%-CI]; p-value	0.93 [0.16, 5.32], 0.9308		1.40 [0.26, 7.58], 0.6940		1.15 [0.34, 3.87], 0.8209	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9316		0.02 [-0.07, 0.11], 0.6811		0.01 [-0.06, 0.07], 0.8173	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	6/73 (8.2)	2/33 (6.1)	13/143 (9.1)	9/72 (12.5)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		1.36 [0.29, 6.37], 0.6994		0.73 [0.33, 1.62], 0.4360	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		1.39 [0.26, 7.27], 0.6969		0.70 [0.28, 1.72], 0.4363	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		0.02 [-0.08, 0.12], 0.6811		-0.03 [-0.12, 0.06], 0.4566	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8351		0.3282		0.3739	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	16/71 (22.5)	10/33 (30.3)	15/71 (21.1)	3/39 (7.7)	31/142 (21.8)	13/72 (18.1)
RR [95%-CI]; p-value	0.74 [0.38, 1.46], 0.3888		2.75 [0.85, 8.91], 0.0923		1.21 [0.68, 2.16], 0.5227	
OR [95%-CI]; p-value	0.67 [0.26, 1.69], 0.3945		3.21 [0.87, 11.89], 0.0685		1.27 [0.62, 2.61], 0.5185	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.11], 0.4092		0.13 [0.01, 0.26], 0.0374		0.04 [-0.07, 0.15], 0.5082	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	12/70 (17.1)	10/39 (25.6)	11/73 (15.1)	4/33 (12.1)	23/143 (16.1)	14/72 (19.4)
RR [95%-CI]; p-value	0.67 [0.32, 1.40], 0.2877		1.24 [0.43, 3.62], 0.6896		0.83 [0.45, 1.51], 0.5361	
OR [95%-CI]; p-value	0.60 [0.23, 1.55], 0.2893		1.29 [0.38, 4.38], 0.6869		0.79 [0.38, 1.66], 0.5378	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.08], 0.3069		0.03 [-0.11, 0.17], 0.6762		-0.03 [-0.14, 0.08], 0.5474	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9269		0.2973		0.4477	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	7/33 (21.2)	7/71 (9.9)	3/39 (7.7)	17/142 (12.0)	10/72 (13.9)
RR [95%-CI]; p-value	0.66 [0.28, 1.59], 0.3580		1.28 [0.35, 4.68], 0.7072		0.86 [0.42, 1.78], 0.6892	
OR [95%-CI]; p-value	0.61 [0.21, 1.77], 0.3603		1.31 [0.32, 5.39], 0.7053		0.84 [0.36, 1.95], 0.6898	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.09], 0.3863		0.02 [-0.09, 0.13], 0.6959		-0.02 [-0.12, 0.08], 0.6958	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	8/39 (20.5)	10/73 (13.7)	8/33 (24.2)	19/143 (13.3)	16/72 (22.2)
RR [95%-CI]; p-value	0.63 [0.26, 1.49], 0.2916		0.57 [0.25, 1.30], 0.1797		0.60 [0.33, 1.09], 0.0939	
OR [95%-CI]; p-value	0.57 [0.20, 1.63], 0.2910		0.50 [0.18, 1.40], 0.1807		0.54 [0.26, 1.12], 0.0939	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3140		-0.11 [-0.27, 0.06], 0.2135		-0.09 [-0.20, 0.02], 0.1146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.3270		0.6637		0.2794	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	25/71 (35.2)	10/33 (30.3)	21/71 (29.6)	10/39 (25.6)	46/142 (32.4)	20/72 (27.8)
RR [95%-CI]; p-value	1.16 [0.63, 2.13], 0.6273		1.15 [0.61, 2.20], 0.6637		1.17 [0.75, 1.81], 0.4952	
OR [95%-CI]; p-value	1.25 [0.51, 3.04], 0.6220		1.22 [0.50, 2.94], 0.6607		1.25 [0.67, 2.33], 0.4896	
RD [95%-CI]; p-value	0.05 [-0.14, 0.24], 0.6167		0.04 [-0.13, 0.21], 0.6563		0.05 [-0.08, 0.18], 0.4829	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	13/70 (18.6)	10/39 (25.6)	12/73 (16.4)	6/33 (18.2)	25/143 (17.5)	16/72 (22.2)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3835		0.90 [0.37, 2.20], 0.8242		0.79 [0.45, 1.38], 0.4011	
OR [95%-CI]; p-value	0.66 [0.26, 1.69], 0.3859		0.89 [0.30, 2.61], 0.8248		0.74 [0.37, 1.50], 0.4038	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.09], 0.3998		-0.02 [-0.17, 0.14], 0.8273		-0.05 [-0.16, 0.07], 0.4169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8173		0.4316		0.5270	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	4/71 (5.6)	2/39 (5.1)	14/142 (9.9)	5/72 (6.9)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.21, 5.73], 0.9112		1.42 [0.53, 3.79], 0.4838	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.10 [0.19, 6.32], 0.9111		1.47 [0.51, 4.24], 0.4788	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.08, 0.09], 0.9099		0.03 [-0.05, 0.11], 0.4552	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	2/39 (5.1)	7/73 (9.6)	1/33 (3.0)	14/143 (9.8)	3/72 (4.2)
RR [95%-CI]; p-value	1.95 [0.43, 8.93], 0.3898		3.16 [0.41, 24.69], 0.2718		2.35 [0.70, 7.91], 0.1680	
OR [95%-CI]; p-value	2.06 [0.41, 10.42], 0.3757		3.39 [0.40, 28.77], 0.2365		2.50 [0.69, 8.98], 0.1493	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3331		0.07 [-0.02, 0.15], 0.1502		0.06 [-0.01, 0.12], 0.1005	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.1992		0.8266		0.2485	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	10/71 (14.1)	3/33 (9.1)	6/71 (8.5)	3/39 (7.7)	16/142 (11.3)	6/72 (8.3)
RR [95%-CI]; p-value	1.55 [0.46, 5.26], 0.4827		1.10 [0.29, 4.15], 0.8898		1.35 [0.55, 3.31], 0.5086	
OR [95%-CI]; p-value	1.64 [0.42, 6.40], 0.4736		1.11 [0.26, 4.70], 0.8896		1.40 [0.52, 3.74], 0.5043	
RD [95%-CI]; p-value	0.05 [-0.08, 0.18], 0.4415		0.01 [-0.10, 0.11], 0.8882		0.03 [-0.05, 0.11], 0.4849	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	7/39 (17.9)	8/73 (11.0)	4/33 (12.1)	15/143 (10.5)	11/72 (15.3)
RR [95%-CI]; p-value	0.56 [0.21, 1.47], 0.2381		0.90 [0.29, 2.79], 0.8609		0.69 [0.33, 1.42], 0.3091	
OR [95%-CI]; p-value	0.51 [0.16, 1.57], 0.2345		0.89 [0.25, 3.20], 0.8612		0.65 [0.28, 1.50], 0.3095	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2639		-0.01 [-0.14, 0.12], 0.8634		-0.05 [-0.14, 0.05], 0.3338	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0323		0.2866		0.3081	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	17/71 (23.9)	6/33 (18.2)	10/71 (14.1)	8/39 (20.5)	27/142 (19.0)	14/72 (19.4)
RR [95%-CI]; p-value	1.32 [0.57, 3.03], 0.5177		0.69 [0.30, 1.60], 0.3824		0.98 [0.55, 1.75], 0.9397	
OR [95%-CI]; p-value	1.42 [0.50, 4.00], 0.5099		0.64 [0.23, 1.77], 0.3833		0.97 [0.47, 2.00], 0.9397	
RD [95%-CI]; p-value	0.06 [-0.11, 0.22], 0.4933		-0.06 [-0.21, 0.09], 0.4021		-0.00 [-0.12, 0.11], 0.9399	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	15/39 (38.5)	15/73 (20.5)	5/33 (15.2)	26/143 (18.2)	20/72 (27.8)
RR [95%-CI]; p-value	0.41 [0.21, 0.80], 0.0091		1.36 [0.54, 3.42], 0.5185		0.65 [0.39, 1.09], 0.1030	
OR [95%-CI]; p-value	0.30 [0.12, 0.74], 0.0076		1.45 [0.48, 4.39], 0.5108		0.58 [0.30, 1.13], 0.1054	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.05], 0.0108		0.05 [-0.10, 0.21], 0.4907		-0.10 [-0.22, 0.03], 0.1208	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5879		0.1012		0.4410	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	13/71 (18.3)	13/33 (39.4)	14/71 (19.7)	6/39 (15.4)	27/142 (19.0)	19/72 (26.4)
RR [95%-CI]; p-value	0.46 [0.24, 0.89], 0.0206		1.28 [0.54, 3.07], 0.5774		0.72 [0.43, 1.20], 0.2112	
OR [95%-CI]; p-value	0.34 [0.14, 0.87], 0.0208		1.35 [0.47, 3.85], 0.5729		0.65 [0.33, 1.28], 0.2146	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.02], 0.0292		0.04 [-0.10, 0.19], 0.5614		-0.07 [-0.19, 0.05], 0.2305	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	10/39 (25.6)	8/73 (11.0)	8/33 (24.2)	19/143 (13.3)	18/72 (25.0)
RR [95%-CI]; p-value	0.61 [0.29, 1.31], 0.2076		0.45 [0.19, 1.10], 0.0802		0.53 [0.30, 0.95], 0.0324	
OR [95%-CI]; p-value	0.54 [0.21, 1.42], 0.2078		0.38 [0.13, 1.14], 0.0769		0.46 [0.22, 0.94], 0.0318	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2280		-0.13 [-0.30, 0.03], 0.1098		-0.12 [-0.23, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9989		0.6150		0.7564	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	7/71 (9.9)	7/33 (21.2)	11/71 (15.5)	4/39 (10.3)	18/142 (12.7)	11/72 (15.3)
RR [95%-CI]; p-value	0.46 [0.18, 1.22], 0.1188		1.51 [0.52, 4.43], 0.4523		0.83 [0.41, 1.66], 0.5983	
OR [95%-CI]; p-value	0.41 [0.13, 1.27], 0.1144		1.60 [0.47, 5.42], 0.4439		0.80 [0.36, 1.81], 0.5993	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.04], 0.1531		0.05 [-0.07, 0.18], 0.4193		-0.03 [-0.13, 0.07], 0.6083	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	9/73 (12.3)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		1.02 [0.34, 3.07], 0.9759		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		1.02 [0.29, 3.58], 0.9759		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		0.00 [-0.13, 0.14], 0.9759		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.4087		0.2542		0.1799	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	1/33 (3.0)	6/71 (8.5)	2/39 (5.1)	11/142 (7.7)	3/72 (4.2)
RR [95%-CI]; p-value	2.32 [0.28, 19.11], 0.4328		1.65 [0.35, 7.78], 0.5281		1.86 [0.54, 6.45], 0.3288	
OR [95%-CI]; p-value	2.42 [0.27, 21.62], 0.4141		1.71 [0.33, 8.90], 0.5209		1.93 [0.52, 7.15], 0.3170	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3460		0.03 [-0.06, 0.13], 0.4919		0.04 [-0.03, 0.10], 0.2711	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	6/70 (8.6)	4/39 (10.3)	6/73 (8.2)	5/33 (15.2)	12/143 (8.4)	9/72 (12.5)
RR [95%-CI]; p-value	0.84 [0.25, 2.78], 0.7700		0.54 [0.18, 1.65], 0.2816		0.67 [0.30, 1.52], 0.3388	
OR [95%-CI]; p-value	0.82 [0.22, 3.10], 0.7702		0.50 [0.14, 1.78], 0.2785		0.64 [0.26, 1.60], 0.3382	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.10], 0.7751		-0.07 [-0.21, 0.07], 0.3234		-0.04 [-0.13, 0.05], 0.3650	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7918		0.1249		0.3349	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	6/33 (18.2)	12/71 (16.9)	3/39 (7.7)	21/142 (14.8)	9/72 (12.5)
RR [95%-CI]; p-value	0.70 [0.27, 1.80], 0.4553		2.20 [0.66, 7.32], 0.1998		1.18 [0.57, 2.45], 0.6506	
OR [95%-CI]; p-value	0.65 [0.21, 2.02], 0.4570		2.44 [0.64, 9.24], 0.1782		1.21 [0.53, 2.81], 0.6486	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4797		0.09 [-0.03, 0.21], 0.1351		0.02 [-0.07, 0.12], 0.6408	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	9/70 (12.9)	6/39 (15.4)	5/73 (6.8)	4/33 (12.1)	14/143 (9.8)	10/72 (13.9)
RR [95%-CI]; p-value	0.84 [0.32, 2.17], 0.7129		0.57 [0.16, 1.97], 0.3703		0.70 [0.33, 1.51], 0.3674	
OR [95%-CI]; p-value	0.81 [0.27, 2.48], 0.7135		0.53 [0.13, 2.13], 0.3673		0.67 [0.28, 1.60], 0.3678	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7191		-0.05 [-0.18, 0.07], 0.4104		-0.04 [-0.13, 0.05], 0.3906	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7563		0.0951		0.0960	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	3/33 (9.1)	7/71 (9.9)	0/39 (0.0)	11/142 (7.7)	3/72 (4.2)
RR [95%-CI]; p-value	0.62 [0.15, 2.61], 0.5145		7.79 [0.45, 133.66], 0.1570		1.86 [0.54, 6.45], 0.3288	
OR [95%-CI]; p-value	0.60 [0.13, 2.83], 0.5125		8.53 [0.47, 154.52], 0.0852		1.93 [0.52, 7.15], 0.3170	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.08], 0.5444		0.09 [0.01, 0.16], 0.0300		0.04 [-0.03, 0.10], 0.2711	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	8/73 (11.0)	6/33 (18.2)	13/143 (9.1)	12/72 (16.7)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		0.60 [0.23, 1.60], 0.3090		0.55 [0.26, 1.13], 0.1045	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		0.55 [0.18, 1.75], 0.3091		0.50 [0.22, 1.16], 0.1020	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		-0.07 [-0.22, 0.08], 0.3448		-0.08 [-0.17, 0.02], 0.1303	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.2.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7336		0.4179		0.7370	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	8/71 (11.3)	5/33 (15.2)	3/71 (4.2)	1/39 (2.6)	11/142 (7.7)	6/72 (8.3)
RR [95%-CI]; p-value	0.74 [0.26, 2.10], 0.5761		1.65 [0.18, 15.31], 0.6605		0.93 [0.36, 2.41], 0.8807	
OR [95%-CI]; p-value	0.71 [0.21, 2.37], 0.5772		1.68 [0.17, 16.68], 0.6561		0.92 [0.33, 2.61], 0.8808	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.10], 0.5938		0.02 [-0.05, 0.08], 0.6330		-0.01 [-0.08, 0.07], 0.8820	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	4/39 (10.3)	8/73 (11.0)	6/33 (18.2)	15/143 (10.5)	10/72 (13.9)
RR [95%-CI]; p-value	0.98 [0.30, 3.12], 0.9660		0.60 [0.23, 1.60], 0.3090		0.76 [0.36, 1.60], 0.4622	
OR [95%-CI]; p-value	0.97 [0.27, 3.55], 0.9660		0.55 [0.18, 1.75], 0.3091		0.73 [0.31, 1.71], 0.4630	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9661		-0.07 [-0.22, 0.08], 0.3448		-0.03 [-0.13, 0.06], 0.4801	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_2_m_soc_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.4.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3715		0.9283		0.4007	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	3/71 (4.2)	8/33 (24.2)	3/71 (4.2)	0/39 (0.0)	6/142 (4.2)	8/72 (11.1)
RR [95%-CI]; p-value	0.17 [0.05, 0.62], 0.0066		3.34 [0.17, 64.97], 0.4261		0.38 [0.14, 1.05], 0.0631	
OR [95%-CI]; p-value	0.14 [0.03, 0.56], 0.0020		3.44 [0.17, 70.49], 0.3946		0.35 [0.12, 1.06], 0.0543	
RD [95%-CI]; p-value	-0.20 [-0.35, -0.05], 0.0106		0.03 [-0.03, 0.09], 0.3202		-0.07 [-0.15, 0.01], 0.0907	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	4/39 (10.3)	3/73 (4.1)	0/33 (0.0)	6/143 (4.2)	4/72 (5.6)
RR [95%-CI]; p-value	0.42 [0.10, 1.77], 0.2365		2.75 [0.14, 53.45], 0.5033		0.76 [0.22, 2.59], 0.6554	
OR [95%-CI]; p-value	0.39 [0.08, 1.85], 0.2229		2.83 [0.14, 58.10], 0.4818		0.74 [0.20, 2.73], 0.6550	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.2713		0.03 [-0.04, 0.09], 0.4029		-0.01 [-0.08, 0.05], 0.6687	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_4_m_pt_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.4.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0996		0.4314		0.3278	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	6/71 (8.5)	4/33 (12.1)	4/71 (5.6)	3/39 (7.7)	10/142 (7.0)	7/72 (9.7)
RR [95%-CI]; p-value	0.70 [0.21, 2.31], 0.5544		0.73 [0.17, 3.11], 0.6727		0.72 [0.29, 1.82], 0.4936	
OR [95%-CI]; p-value	0.67 [0.18, 2.55], 0.5545		0.72 [0.15, 3.38], 0.6722		0.70 [0.26, 1.93], 0.4933	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5764		-0.02 [-0.12, 0.08], 0.6847		-0.03 [-0.11, 0.05], 0.5132	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	1/70 (1.4)	6/39 (15.4)	3/73 (4.1)	0/33 (0.0)	4/143 (2.8)	6/72 (8.3)
RR [95%-CI]; p-value	0.09 [0.01, 0.74], 0.0252		2.75 [0.14, 53.45], 0.5033		0.34 [0.10, 1.15], 0.0827	
OR [95%-CI]; p-value	0.08 [0.01, 0.69], 0.0044		2.83 [0.14, 58.10], 0.4818		0.32 [0.09, 1.16], 0.0689	
RD [95%-CI]; p-value	-0.14 [-0.26, -0.02], 0.0190		0.03 [-0.04, 0.09], 0.4029		-0.06 [-0.12, 0.01], 0.1175	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_4_m_pt_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.4.s2
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.2103		0.5972		0.7253	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	4/33 (12.1)	2/71 (2.8)	1/39 (2.6)	7/142 (4.9)	5/72 (6.9)
RR [95%-CI]; p-value	0.58 [0.17, 2.02], 0.3939		1.10 [0.10, 11.73], 0.9380		0.71 [0.23, 2.16], 0.5459	
OR [95%-CI]; p-value	0.55 [0.14, 2.19], 0.3912		1.10 [0.10, 12.55], 0.9379		0.69 [0.21, 2.27], 0.5450	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4305		0.00 [-0.06, 0.07], 0.9371		-0.02 [-0.09, 0.05], 0.5652	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	1/39 (2.6)	6/73 (8.2)	5/33 (15.2)	11/143 (7.7)	6/72 (8.3)
RR [95%-CI]; p-value	2.79 [0.34, 23.00], 0.3415		0.54 [0.18, 1.65], 0.2816		0.92 [0.36, 2.40], 0.8693	
OR [95%-CI]; p-value	2.92 [0.33, 25.96], 0.3150		0.50 [0.14, 1.78], 0.2785		0.92 [0.32, 2.59], 0.8694	
RD [95%-CI]; p-value	0.05 [-0.03, 0.12], 0.2506		-0.07 [-0.21, 0.07], 0.3234		-0.01 [-0.08, 0.07], 0.8710	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_4_m_pt_ae1pct_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.8797		0.7901		0.6007	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	1/33 (3.0)	4/71 (5.6)	3/39 (7.7)	13/142 (9.2)	4/72 (5.6)
RR [95%-CI]; p-value	4.18 [0.55, 31.67], 0.1659		0.73 [0.17, 3.11], 0.6727		1.65 [0.56, 4.87], 0.3665	
OR [95%-CI]; p-value	4.65 [0.56, 38.30], 0.1204		0.72 [0.15, 3.38], 0.6722		1.71 [0.54, 5.46], 0.3576	
RD [95%-CI]; p-value	0.10 [-0.00, 0.19], 0.0513		-0.02 [-0.12, 0.08], 0.6847		0.04 [-0.04, 0.11], 0.3208	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	6/70 (8.6)	1/39 (2.6)	5/73 (6.8)	4/33 (12.1)	11/143 (7.7)	5/72 (6.9)
RR [95%-CI]; p-value	3.34 [0.42, 26.77], 0.2556		0.57 [0.16, 1.97], 0.3703		1.11 [0.40, 3.07], 0.8440	
OR [95%-CI]; p-value	3.56 [0.41, 30.73], 0.2201		0.53 [0.13, 2.13], 0.3673		1.12 [0.37, 3.35], 0.8437	
RD [95%-CI]; p-value	0.06 [-0.02, 0.14], 0.1522		-0.05 [-0.18, 0.07], 0.4104		0.01 [-0.07, 0.08], 0.8412	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5348		0.6179		0.2794	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	0/71 (0.0)	0/33 (0.0)	0/71 (0.0)	1/39 (2.6)	0/142 (0.0)	1/72 (1.4)
RR [95%-CI]; p-value	NA		0.27 [0.01, 7.95], 0.4502		0.25 [0.01, 7.44], 0.4254	
OR [95%-CI]; p-value	NA		0.27 [0.01, 8.16], 0.4182		0.25 [0.01, 7.54], 0.3890	
RD [95%-CI]; p-value	NA		-0.02 [-0.07, 0.03], 0.4924		-0.01 [-0.04, 0.02], 0.4787	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	2/70 (2.9)	0/39 (0.0)	1/73 (1.4)	0/33 (0.0)	3/143 (2.1)	0/72 (0.0)
RR [95%-CI]; p-value	2.26 [0.10, 48.83], 0.6038		0.92 [0.03, 26.69], 0.9602		3.04 [0.15, 59.92], 0.4644	
OR [95%-CI]; p-value	2.29 [0.10, 52.16], 0.5924		0.92 [0.03, 28.01], 0.9602		3.09 [0.15, 62.44], 0.4397	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5512		-0.00 [-0.05, 0.05], 0.9608		0.01 [-0.02, 0.04], 0.3614	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.6764		0.4109		0.2282	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	9/71 (12.7)	1/33 (3.0)	4/71 (5.6)	2/39 (5.1)	13/142 (9.2)	3/72 (4.2)
RR [95%-CI]; p-value	4.18 [0.55, 31.67], 0.1659		1.10 [0.21, 5.73], 0.9112		2.20 [0.65, 7.46], 0.2071	
OR [95%-CI]; p-value	4.65 [0.56, 38.30], 0.1204		1.10 [0.19, 6.32], 0.9111		2.32 [0.64, 8.41], 0.1899	
RD [95%-CI]; p-value	0.10 [-0.00, 0.19], 0.0513		0.01 [-0.08, 0.09], 0.9099		0.05 [-0.02, 0.12], 0.1396	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	4/70 (5.7)	1/39 (2.6)	4/73 (5.5)	4/33 (12.1)	8/143 (5.6)	5/72 (6.9)
RR [95%-CI]; p-value	2.23 [0.26, 19.25], 0.4663		0.45 [0.12, 1.70], 0.2397		0.81 [0.27, 2.37], 0.6951	
OR [95%-CI]; p-value	2.30 [0.25, 21.36], 0.4511		0.42 [0.10, 1.80], 0.2307		0.79 [0.25, 2.52], 0.6951	
RD [95%-CI]; p-value	0.03 [-0.04, 0.11], 0.4016		-0.07 [-0.19, 0.06], 0.2898		-0.01 [-0.08, 0.06], 0.7045	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.7486		0.8297		0.7053	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	4/71 (5.6)	1/33 (3.0)	1/71 (1.4)	0/39 (0.0)	5/142 (3.5)	1/72 (1.4)
RR [95%-CI]; p-value	1.86 [0.22, 15.99], 0.5722		1.11 [0.04, 32.43], 0.9505		2.54 [0.30, 21.30], 0.3916	
OR [95%-CI]; p-value	1.91 [0.21, 17.79], 0.5635		1.11 [0.04, 33.97], 0.9505		2.59 [0.30, 22.61], 0.3720	
RD [95%-CI]; p-value	0.03 [-0.05, 0.11], 0.5202		0.00 [-0.04, 0.05], 0.9497		0.02 [-0.02, 0.06], 0.3035	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	0/39 (0.0)	2/73 (2.7)	0/33 (0.0)	5/143 (3.5)	0/72 (0.0)
RR [95%-CI]; p-value	3.39 [0.17, 65.89], 0.4207		1.84 [0.09, 39.62], 0.6984		5.07 [0.28, 91.53], 0.2715	
OR [95%-CI]; p-value	3.49 [0.17, 71.55], 0.3883		1.86 [0.08, 42.37], 0.6930		5.22 [0.28, 96.84], 0.2170	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3148		0.01 [-0.04, 0.07], 0.6600		0.03 [-0.01, 0.06], 0.1226	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8404		0.9394		0.8494	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	3/33 (9.1)	4/71 (5.6)	2/39 (5.1)	9/142 (6.3)	5/72 (6.9)
RR [95%-CI]; p-value	0.77 [0.20, 3.05], 0.7150		1.10 [0.21, 5.73], 0.9112		0.91 [0.32, 2.62], 0.8653	
OR [95%-CI]; p-value	0.76 [0.17, 3.38], 0.7152		1.10 [0.19, 6.32], 0.9111		0.91 [0.29, 2.81], 0.8654	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.09], 0.7263		0.01 [-0.08, 0.09], 0.9099		-0.01 [-0.08, 0.07], 0.8672	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	7/70 (10.0)	6/39 (15.4)	9/73 (12.3)	4/33 (12.1)	16/143 (11.2)	10/72 (13.9)
RR [95%-CI]; p-value	0.65 [0.23, 1.80], 0.4067		1.02 [0.34, 3.07], 0.9759		0.81 [0.39, 1.68], 0.5657	
OR [95%-CI]; p-value	0.61 [0.19, 1.97], 0.4057		1.02 [0.29, 3.58], 0.9759		0.78 [0.34, 1.82], 0.5666	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.08], 0.4284		0.00 [-0.13, 0.14], 0.9759		-0.03 [-0.12, 0.07], 0.5780	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5348		0.9235		0.6581	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	0/71 (0.0)	0/33 (0.0)	1/71 (1.4)	0/39 (0.0)	1/142 (0.7)	0/72 (0.0)
RR [95%-CI]; p-value	NA		1.11 [0.04, 32.43], 0.9505		1.02 [0.03, 30.08], 0.9903	
OR [95%-CI]; p-value	NA		1.11 [0.04, 33.97], 0.9505		1.02 [0.03, 30.80], 0.9903	
RD [95%-CI]; p-value	NA		0.00 [-0.04, 0.05], 0.9497		0.00 [-0.02, 0.02], 0.9903	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	2/70 (2.9)	0/39 (0.0)	3/73 (4.1)	1/33 (3.0)	5/143 (3.5)	1/72 (1.4)
RR [95%-CI]; p-value	2.26 [0.10, 48.83], 0.6038		1.36 [0.15, 12.56], 0.7885		2.52 [0.30, 21.15], 0.3952	
OR [95%-CI]; p-value	2.29 [0.10, 52.16], 0.5924		1.37 [0.14, 13.70], 0.7872		2.57 [0.29, 22.44], 0.3759	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5512		0.01 [-0.06, 0.08], 0.7754		0.02 [-0.02, 0.06], 0.3073	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.5708		0.9696		0.6661	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	5/71 (7.0)	3/33 (9.1)	3/71 (4.2)	2/39 (5.1)	8/142 (5.6)	5/72 (6.9)
RR [95%-CI]; p-value	0.77 [0.20, 3.05], 0.7150		0.82 [0.14, 4.72], 0.8279		0.81 [0.28, 2.39], 0.7045	
OR [95%-CI]; p-value	0.76 [0.17, 3.38], 0.7152		0.82 [0.13, 5.11], 0.8278		0.80 [0.25, 2.54], 0.7045	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.09], 0.7263		-0.01 [-0.09, 0.07], 0.8323		-0.01 [-0.08, 0.06], 0.7132	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	5/70 (7.1)	6/39 (15.4)	7/73 (9.6)	4/33 (12.1)	12/143 (8.4)	10/72 (13.9)
RR [95%-CI]; p-value	0.46 [0.15, 1.42], 0.1795		0.79 [0.25, 2.52], 0.6916		0.60 [0.27, 1.33], 0.2113	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1709		0.77 [0.21, 2.83], 0.6922		0.57 [0.23, 1.39], 0.2094	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2080		-0.03 [-0.16, 0.10], 0.7032		-0.05 [-0.15, 0.04], 0.2410	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.7.s2
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.7886		0.8120		0.9397	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	2/71 (2.8)	0/33 (0.0)	1/71 (1.4)	0/39 (0.0)	3/142 (2.1)	0/72 (0.0)
RR [95%-CI]; p-value	1.89 [0.09, 40.72], 0.6853		1.11 [0.04, 32.43], 0.9505		3.06 [0.16, 60.34], 0.4616	
OR [95%-CI]; p-value	1.91 [0.08, 43.61], 0.6793		1.11 [0.04, 33.97], 0.9505		3.11 [0.15, 62.89], 0.4365	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.6446		0.00 [-0.04, 0.05], 0.9497		0.01 [-0.02, 0.04], 0.3584	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	3/70 (4.3)	0/39 (0.0)	4/73 (5.5)	1/33 (3.0)	7/143 (4.9)	1/72 (1.4)
RR [95%-CI]; p-value	3.39 [0.17, 65.89], 0.4207		1.81 [0.21, 15.56], 0.5896		3.52 [0.44, 28.10], 0.2343	
OR [95%-CI]; p-value	3.49 [0.17, 71.55], 0.3883		1.86 [0.20, 17.27], 0.5818		3.65 [0.44, 30.29], 0.1999	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3148		0.02 [-0.05, 0.10], 0.5403		0.04 [-0.01, 0.08], 0.1226	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_7_m_pt_smq_sex.sas using SAS 9.4

Table 12.4.4.1.6.s2
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.4079		0.8723		0.6233	
1.Female	N1=71	N1=33	N1=71	N1=39	N1=142	N1=72
n/N1 (%)	13/71 (18.3)	11/33 (33.3)	15/71 (21.1)	5/39 (12.8)	28/142 (19.7)	16/72 (22.2)
RR [95%-CI]; p-value	0.55 [0.28, 1.09], 0.0882		1.65 [0.65, 4.19], 0.2944		0.89 [0.51, 1.53], 0.6672	
OR [95%-CI]; p-value	0.45 [0.17, 1.15], 0.0906		1.82 [0.61, 5.46], 0.2799		0.86 [0.43, 1.72], 0.6685	
RD [95%-CI]; p-value	-0.15 [-0.33, 0.03], 0.1101		0.08 [-0.06, 0.22], 0.2500		-0.03 [-0.14, 0.09], 0.6728	
2.Male	N2=70	N2=39	N2=73	N2=33	N2=143	N2=72
n/N2 (%)	11/70 (15.7)	7/39 (17.9)	13/73 (17.8)	4/33 (12.1)	24/143 (16.8)	11/72 (15.3)
RR [95%-CI]; p-value	0.88 [0.37, 2.08], 0.7627		1.47 [0.52, 4.17], 0.4695		1.10 [0.57, 2.11], 0.7786	
OR [95%-CI]; p-value	0.85 [0.30, 2.41], 0.7633		1.57 [0.47, 5.24], 0.4600		1.12 [0.51, 2.43], 0.7778	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.13], 0.7666		0.06 [-0.08, 0.20], 0.4318		0.02 [-0.09, 0.12], 0.7750	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex/T12_4_4_1_6_m_pt_adr_sex.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.4273		0.2512		0.2367	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	52/73 (71.2)	26/36 (72.2)	49/77 (63.6)	15/29 (51.7)	101/150 (67.3)	41/65 (63.1)
RR [95%-CI]; p-value	0.99 [0.77, 1.27], 0.9137		1.23 [0.83, 1.82], 0.2977		1.07 [0.86, 1.33], 0.5550	
OR [95%-CI]; p-value	0.95 [0.39, 2.31], 0.9142		1.63 [0.69, 3.87], 0.2636		1.21 [0.66, 2.22], 0.5450	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9139		0.12 [-0.09, 0.33], 0.2690		0.04 [-0.10, 0.18], 0.5492	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	49/68 (72.1)	30/36 (83.3)	42/67 (62.7)	29/43 (67.4)	91/135 (67.4)	59/79 (74.7)
RR [95%-CI]; p-value	0.86 [0.70, 1.06], 0.1707		0.93 [0.70, 1.23], 0.6061		0.90 [0.76, 1.07], 0.2480	
OR [95%-CI]; p-value	0.52 [0.19, 1.44], 0.2005		0.81 [0.36, 1.82], 0.6109		0.70 [0.38, 1.31], 0.2619	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.05], 0.1721		-0.05 [-0.23, 0.13], 0.6081		-0.07 [-0.20, 0.05], 0.2512	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.7123		0.3201		0.2391	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	11/77 (14.3)	2/29 (6.9)	21/150 (14.0)	9/65 (13.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		2.07 [0.49, 8.79], 0.3232		1.01 [0.49, 2.09], 0.9762	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		2.25 [0.47, 10.83], 0.3012		1.01 [0.44, 2.35], 0.9761	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		0.07 [-0.05, 0.19], 0.2309		0.00 [-0.10, 0.10], 0.9761	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	4/36 (11.1)	8/67 (11.9)	0/43 (0.0)	15/135 (11.1)	4/79 (5.1)
RR [95%-CI]; p-value	0.93 [0.29, 2.96], 0.8973		10.39 [0.61, 176.30], 0.1052		2.19 [0.75, 6.38], 0.1490	
OR [95%-CI]; p-value	0.92 [0.25, 3.37], 0.8974		11.66 [0.65, 208.57], 0.0375		2.34 [0.75, 7.33], 0.1333	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.8985		0.11 [0.02, 0.19], 0.0117		0.06 [-0.01, 0.13], 0.0985	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.2083		0.3010		0.9961	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	5/36 (13.9)	5/77 (6.5)	1/29 (3.4)	15/150 (10.0)	6/65 (9.2)
RR [95%-CI]; p-value	0.99 [0.36, 2.67], 0.9784		1.88 [0.23, 15.44], 0.5555		1.08 [0.44, 2.67], 0.8618	
OR [95%-CI]; p-value	0.98 [0.31, 3.13], 0.9784		1.94 [0.22, 17.39], 0.5453		1.09 [0.40, 2.95], 0.8615	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.14], 0.9784		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.08, 0.09], 0.8595	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	1/36 (2.8)	5/67 (7.5)	6/43 (14.0)	13/135 (9.6)	7/79 (8.9)
RR [95%-CI]; p-value	4.24 [0.55, 32.55], 0.1653		0.53 [0.17, 1.64], 0.2749		1.09 [0.45, 2.61], 0.8523	
OR [95%-CI]; p-value	4.67 [0.56, 38.89], 0.1210		0.50 [0.14, 1.74], 0.2682		1.10 [0.42, 2.87], 0.8521	
RD [95%-CI]; p-value	0.09 [-0.00, 0.18], 0.0596		-0.06 [-0.19, 0.06], 0.2938		0.01 [-0.07, 0.09], 0.8506	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.4535		0.2761		0.2185	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	14/73 (19.2)	4/36 (11.1)	13/77 (16.9)	3/29 (10.3)	27/150 (18.0)	7/65 (10.8)
RR [95%-CI]; p-value	1.73 [0.61, 4.87], 0.3023		1.63 [0.50, 5.31], 0.4161		1.67 [0.77, 3.64], 0.1960	
OR [95%-CI]; p-value	1.90 [0.58, 6.25], 0.2861		1.76 [0.46, 6.69], 0.4019		1.82 [0.75, 4.42], 0.1820	
RD [95%-CI]; p-value	0.08 [-0.06, 0.22], 0.2475		0.07 [-0.07, 0.20], 0.3561		0.07 [-0.02, 0.17], 0.1451	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	16/68 (23.5)	8/36 (22.2)	9/67 (13.4)	8/43 (18.6)	25/135 (18.5)	16/79 (20.3)
RR [95%-CI]; p-value	1.06 [0.50, 2.23], 0.8807		0.72 [0.30, 1.73], 0.4641		0.91 [0.52, 1.61], 0.7551	
OR [95%-CI]; p-value	1.08 [0.41, 2.83], 0.8803		0.68 [0.24, 1.92], 0.4640		0.89 [0.44, 1.80], 0.7557	
RD [95%-CI]; p-value	0.01 [-0.16, 0.18], 0.8796		-0.05 [-0.19, 0.09], 0.4757		-0.02 [-0.13, 0.09], 0.7577	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.4675		0.3116		0.8734	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	7/73 (9.6)	3/36 (8.3)	10/77 (13.0)	1/29 (3.4)	17/150 (11.3)	4/65 (6.2)
RR [95%-CI]; p-value	1.15 [0.32, 4.19], 0.8314		3.77 [0.50, 28.13], 0.1962		1.84 [0.64, 5.26], 0.2541	
OR [95%-CI]; p-value	1.17 [0.28, 4.81], 0.8309		4.18 [0.51, 34.21], 0.1511		1.95 [0.63, 6.04], 0.2400	
RD [95%-CI]; p-value	0.01 [-0.10, 0.13], 0.8272		0.10 [-0.00, 0.20], 0.0622		0.05 [-0.03, 0.13], 0.1895	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	2/36 (5.6)	5/67 (7.5)	3/43 (7.0)	14/135 (10.4)	5/79 (6.3)
RR [95%-CI]; p-value	2.38 [0.54, 10.44], 0.2497		1.07 [0.27, 4.25], 0.9238		1.64 [0.61, 4.38], 0.3247	
OR [95%-CI]; p-value	2.59 [0.53, 12.71], 0.2257		1.08 [0.24, 4.75], 0.9237		1.71 [0.59, 4.95], 0.3159	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1710		0.00 [-0.09, 0.10], 0.9232		0.04 [-0.03, 0.11], 0.2867	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.3890		0.3528		0.8167	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	2/36 (5.6)	4/77 (5.2)	0/29 (0.0)	8/150 (5.3)	2/65 (3.1)
RR [95%-CI]; p-value	0.99 [0.19, 5.13], 0.9869		3.06 [0.17, 56.21], 0.4505		1.73 [0.38, 7.94], 0.4787	
OR [95%-CI]; p-value	0.99 [0.17, 5.65], 0.9869		3.18 [0.16, 62.02], 0.4217		1.77 [0.37, 8.60], 0.4706	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.09], 0.9870		0.03 [-0.03, 0.10], 0.3132		0.02 [-0.03, 0.08], 0.4237	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	0/36 (0.0)	3/67 (4.5)	3/43 (7.0)	7/135 (5.2)	3/79 (3.8)
RR [95%-CI]; p-value	4.29 [0.23, 79.01], 0.3267		0.64 [0.14, 3.04], 0.5759		1.37 [0.36, 5.13], 0.6447	
OR [95%-CI]; p-value	4.50 [0.23, 87.55], 0.2787		0.63 [0.12, 3.25], 0.5733		1.39 [0.35, 5.52], 0.6425	
RD [95%-CI]; p-value	0.05 [-0.02, 0.11], 0.1898		-0.02 [-0.12, 0.07], 0.5897		0.01 [-0.04, 0.07], 0.6293	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.4839		0.8060		0.5460	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	1/73 (1.4)	1/36 (2.8)	1/77 (1.3)	0/29 (0.0)	2/150 (1.3)	1/65 (1.5)
RR [95%-CI]; p-value	0.49 [0.03, 7.66], 0.6135		0.77 [0.03, 22.24], 0.8769		0.87 [0.08, 9.39], 0.9063	
OR [95%-CI]; p-value	0.49 [0.03, 8.00], 0.6065		0.76 [0.02, 23.37], 0.8766		0.86 [0.08, 9.71], 0.9063	
RD [95%-CI]; p-value	-0.01 [-0.07, 0.05], 0.6452		-0.00 [-0.06, 0.05], 0.8835		-0.00 [-0.04, 0.03], 0.9088	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	0/36 (0.0)	2/67 (3.0)	1/43 (2.3)	4/135 (3.0)	1/79 (1.3)
RR [95%-CI]; p-value	2.15 [0.10, 46.38], 0.6260		1.28 [0.12, 13.73], 0.8364		2.34 [0.27, 20.58], 0.4432	
OR [95%-CI]; p-value	2.18 [0.10, 49.68], 0.6163		1.29 [0.11, 14.70], 0.8358		2.38 [0.26, 21.69], 0.4277	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5761		0.01 [-0.05, 0.07], 0.8315		0.02 [-0.02, 0.05], 0.3784	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.5576		0.1409		0.2253	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	45/73 (61.6)	25/36 (69.4)	39/77 (50.6)	11/29 (37.9)	84/150 (56.0)	36/65 (55.4)
RR [95%-CI]; p-value	0.89 [0.67, 1.18], 0.4081		1.34 [0.80, 2.24], 0.2713		1.01 [0.78, 1.31], 0.9337	
OR [95%-CI]; p-value	0.71 [0.30, 1.66], 0.4243		1.68 [0.70, 4.02], 0.2423		1.03 [0.57, 1.84], 0.9335	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.11], 0.4144		0.13 [-0.08, 0.34], 0.2329		0.01 [-0.14, 0.15], 0.9335	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	37/68 (54.4)	25/36 (69.4)	31/67 (46.3)	24/43 (55.8)	68/135 (50.4)	49/79 (62.0)
RR [95%-CI]; p-value	0.78 [0.58, 1.07], 0.1194		0.83 [0.57, 1.20], 0.3212		0.81 [0.64, 1.03], 0.0898	
OR [95%-CI]; p-value	0.53 [0.22, 1.23], 0.1372		0.68 [0.32, 1.47], 0.3286		0.62 [0.35, 1.09], 0.0984	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.04], 0.1238		-0.10 [-0.29, 0.10], 0.3260		-0.12 [-0.25, 0.02], 0.0937	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.9489		0.9309		0.9440	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	23/73 (31.5)	13/36 (36.1)	26/77 (33.8)	7/29 (24.1)	49/150 (32.7)	20/65 (30.8)
RR [95%-CI]; p-value	0.87 [0.50, 1.51], 0.6273		1.40 [0.68, 2.87], 0.3589		1.06 [0.69, 1.63], 0.7855	
OR [95%-CI]; p-value	0.81 [0.35, 1.89], 0.6307		1.60 [0.61, 4.24], 0.3399		1.09 [0.58, 2.04], 0.7843	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6342		0.10 [-0.09, 0.28], 0.3160		0.02 [-0.12, 0.15], 0.7829	
2.Baseline Weight ≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	27/68 (39.7)	16/36 (44.4)	23/67 (34.3)	11/43 (25.6)	50/135 (37.0)	27/79 (34.2)
RR [95%-CI]; p-value	0.89 [0.56, 1.43], 0.6369		1.34 [0.73, 2.46], 0.3430		1.08 [0.74, 1.58], 0.6760	
OR [95%-CI]; p-value	0.82 [0.36, 1.86], 0.6406		1.52 [0.65, 3.56], 0.3327		1.13 [0.63, 2.03], 0.6740	
RD [95%-CI]; p-value	-0.05 [-0.25, 0.15], 0.6418		0.09 [-0.09, 0.26], 0.3217		0.03 [-0.10, 0.16], 0.6724	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.3.1.s3
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.2083		0.3010		0.9961	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	5/36 (13.9)	5/77 (6.5)	1/29 (3.4)	15/150 (10.0)	6/65 (9.2)
RR [95%-CI]; p-value	0.99 [0.36, 2.67], 0.9784		1.88 [0.23, 15.44], 0.5555		1.08 [0.44, 2.67], 0.8618	
OR [95%-CI]; p-value	0.98 [0.31, 3.13], 0.9784		1.94 [0.22, 17.39], 0.5453		1.09 [0.40, 2.95], 0.8615	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.14], 0.9784		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.08, 0.09], 0.8595	
2.Baseline Weight ≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	1/36 (2.8)	5/67 (7.5)	6/43 (14.0)	13/135 (9.6)	7/79 (8.9)
RR [95%-CI]; p-value	4.24 [0.55, 32.55], 0.1653		0.53 [0.17, 1.64], 0.2749		1.09 [0.45, 2.61], 0.8523	
OR [95%-CI]; p-value	4.67 [0.56, 38.89], 0.1210		0.50 [0.14, 1.74], 0.2682		1.10 [0.42, 2.87], 0.8521	
RD [95%-CI]; p-value	0.09 [-0.00, 0.18], 0.0596		-0.06 [-0.19, 0.06], 0.2938		0.01 [-0.07, 0.09], 0.8506	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_3_1_m_sf_ttl_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6190		0.7629		0.6433	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	3/36 (8.3)	5/77 (6.5)	1/29 (3.4)	10/150 (6.7)	4/65 (6.2)
RR [95%-CI]; p-value	0.82 [0.21, 3.25], 0.7798		1.88 [0.23, 15.44], 0.5555		1.08 [0.35, 3.33], 0.8888	
OR [95%-CI]; p-value	0.81 [0.18, 3.59], 0.7799		1.94 [0.22, 17.39], 0.5453		1.09 [0.33, 3.61], 0.8887	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.09], 0.7863		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.07, 0.08], 0.8870	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	6/67 (9.0)	3/43 (7.0)	12/135 (8.9)	9/79 (11.4)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		1.28 [0.34, 4.86], 0.7133		0.78 [0.34, 1.77], 0.5524	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		1.31 [0.31, 5.55], 0.7118		0.76 [0.30, 1.89], 0.5525	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		0.02 [-0.08, 0.12], 0.7047		-0.03 [-0.11, 0.06], 0.5634	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1702		0.9337		0.6054	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	18/73 (24.7)	9/36 (25.0)	11/77 (14.3)	2/29 (6.9)	29/150 (19.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.99 [0.49, 1.97], 0.9689		2.07 [0.49, 8.79], 0.3232		1.14 [0.61, 2.15], 0.6787	
OR [95%-CI]; p-value	0.98 [0.39, 2.47], 0.9689		2.25 [0.47, 10.83], 0.3012		1.18 [0.55, 2.53], 0.6766	
RD [95%-CI]; p-value	-0.00 [-0.18, 0.17], 0.9690		0.07 [-0.05, 0.19], 0.2309		0.02 [-0.09, 0.14], 0.6702	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	10/68 (14.7)	11/36 (30.6)	15/67 (22.4)	5/43 (11.6)	25/135 (18.5)	16/79 (20.3)
RR [95%-CI]; p-value	0.48 [0.23, 1.02], 0.0577		1.93 [0.75, 4.91], 0.1705		0.91 [0.52, 1.61], 0.7551	
OR [95%-CI]; p-value	0.39 [0.15, 1.04], 0.0554		2.19 [0.73, 6.55], 0.1534		0.89 [0.44, 1.80], 0.7557	
RD [95%-CI]; p-value	-0.16 [-0.33, 0.01], 0.0716		0.11 [-0.03, 0.25], 0.1274		-0.02 [-0.13, 0.09], 0.7577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7893		0.6563		0.8313	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	7/77 (9.1)	4/29 (13.8)	17/150 (11.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		0.66 [0.21, 2.09], 0.4781		0.67 [0.33, 1.35], 0.2618	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		0.63 [0.17, 2.32], 0.4791		0.63 [0.28, 1.43], 0.2634	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		-0.05 [-0.19, 0.09], 0.5133		-0.06 [-0.16, 0.05], 0.2936	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	8/36 (22.2)	10/67 (14.9)	7/43 (16.3)	19/135 (14.1)	15/79 (19.0)
RR [95%-CI]; p-value	0.60 [0.25, 1.41], 0.2389		0.92 [0.38, 2.23], 0.8478		0.74 [0.40, 1.37], 0.3418	
OR [95%-CI]; p-value	0.53 [0.19, 1.53], 0.2384		0.90 [0.32, 2.58], 0.8480		0.70 [0.33, 1.47], 0.3427	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2646		-0.01 [-0.15, 0.13], 0.8491		-0.05 [-0.15, 0.06], 0.3568	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.4851		0.7103		0.8532	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	19/73 (26.0)	8/36 (22.2)	15/77 (19.5)	6/29 (20.7)	34/150 (22.7)	14/65 (21.5)
RR [95%-CI]; p-value	1.17 [0.57, 2.41], 0.6684		0.94 [0.40, 2.19], 0.8889		1.05 [0.61, 1.82], 0.8557	
OR [95%-CI]; p-value	1.23 [0.48, 3.16], 0.6651		0.93 [0.32, 2.68], 0.8893		1.07 [0.53, 2.16], 0.8552	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6591		-0.01 [-0.18, 0.16], 0.8904		0.01 [-0.11, 0.13], 0.8542	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	19/68 (27.9)	12/36 (33.3)	18/67 (26.9)	10/43 (23.3)	37/135 (27.4)	22/79 (27.8)
RR [95%-CI]; p-value	0.84 [0.46, 1.53], 0.5639		1.16 [0.59, 2.26], 0.6736		0.98 [0.63, 1.54], 0.9445	
OR [95%-CI]; p-value	0.78 [0.32, 1.86], 0.5674		1.21 [0.50, 2.95], 0.6715		0.98 [0.53, 1.82], 0.9445	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.13], 0.5726		0.04 [-0.13, 0.20], 0.6680		-0.00 [-0.13, 0.12], 0.9446	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.9043		0.4341		0.5118	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	3/36 (8.3)	6/77 (7.8)	2/29 (6.9)	16/150 (10.7)	5/65 (7.7)
RR [95%-CI]; p-value	1.64 [0.48, 5.61], 0.4272		1.13 [0.24, 5.28], 0.8767		1.39 [0.53, 3.63], 0.5050	
OR [95%-CI]; p-value	1.75 [0.45, 6.78], 0.4163		1.14 [0.22, 6.00], 0.8763		1.43 [0.50, 4.09], 0.4999	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3804		0.01 [-0.10, 0.12], 0.8732		0.03 [-0.05, 0.11], 0.4742	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	2/36 (5.6)	5/67 (7.5)	1/43 (2.3)	12/135 (8.9)	3/79 (3.8)
RR [95%-CI]; p-value	1.85 [0.41, 8.46], 0.4260		3.21 [0.39, 26.54], 0.2794		2.34 [0.68, 8.04], 0.1769	
OR [95%-CI]; p-value	1.95 [0.38, 9.92], 0.4135		3.39 [0.38, 30.04], 0.2470		2.47 [0.68, 9.04], 0.1592	
RD [95%-CI]; p-value	0.05 [-0.06, 0.15], 0.3718		0.05 [-0.03, 0.13], 0.1932		0.05 [-0.01, 0.11], 0.1183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2208		0.4662		0.1763	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	11/73 (15.1)	4/36 (11.1)	10/77 (13.0)	3/29 (10.3)	21/150 (14.0)	7/65 (10.8)
RR [95%-CI]; p-value	1.36 [0.46, 3.96], 0.5777		1.26 [0.37, 4.24], 0.7142		1.30 [0.58, 2.91], 0.5226	
OR [95%-CI]; p-value	1.42 [0.42, 4.81], 0.5727		1.29 [0.33, 5.08], 0.7116		1.35 [0.54, 3.35], 0.5180	
RD [95%-CI]; p-value	0.04 [-0.09, 0.17], 0.5551		0.03 [-0.11, 0.16], 0.6989		0.03 [-0.06, 0.13], 0.4988	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	4/67 (6.0)	4/43 (9.3)	10/135 (7.4)	10/79 (12.7)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.17, 2.43], 0.5140		0.59 [0.25, 1.34], 0.2065	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.62 [0.15, 2.62], 0.5114		0.55 [0.22, 1.39], 0.2028	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.03 [-0.14, 0.07], 0.5289		-0.05 [-0.14, 0.03], 0.2293	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.8092		0.7112		0.9625	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	16/73 (21.9)	11/36 (30.6)	10/77 (13.0)	3/29 (10.3)	26/150 (17.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.72 [0.37, 1.38], 0.3207		1.26 [0.37, 4.24], 0.7142		0.80 [0.45, 1.44], 0.4636	
OR [95%-CI]; p-value	0.64 [0.26, 1.57], 0.3258		1.29 [0.33, 5.08], 0.7116		0.76 [0.37, 1.58], 0.4668	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3413		0.03 [-0.11, 0.16], 0.6989		-0.04 [-0.16, 0.07], 0.4806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	12/68 (17.6)	10/36 (27.8)	15/67 (22.4)	10/43 (23.3)	27/135 (20.0)	20/79 (25.3)
RR [95%-CI]; p-value	0.64 [0.30, 1.33], 0.2267		0.96 [0.48, 1.94], 0.9155		0.79 [0.48, 1.31], 0.3624	
OR [95%-CI]; p-value	0.56 [0.21, 1.45], 0.2288		0.95 [0.38, 2.37], 0.9156		0.74 [0.38, 1.43], 0.3646	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.07], 0.2486		-0.01 [-0.17, 0.15], 0.9158		-0.05 [-0.17, 0.06], 0.3741	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4955		0.0291		0.0732	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	15/73 (20.5)	12/36 (33.3)	14/77 (18.2)	2/29 (6.9)	29/150 (19.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.62 [0.32, 1.18], 0.1419		2.64 [0.64, 10.89], 0.1805		0.90 [0.51, 1.58], 0.7092	
OR [95%-CI]; p-value	0.52 [0.21, 1.27], 0.1459		3.00 [0.64, 14.12], 0.1479		0.87 [0.43, 1.79], 0.7105	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1632		0.11 [-0.01, 0.24], 0.0797		-0.02 [-0.14, 0.10], 0.7147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	11/36 (30.6)	8/67 (11.9)	12/43 (27.9)	17/135 (12.6)	23/79 (29.1)
RR [95%-CI]; p-value	0.43 [0.20, 0.95], 0.0362		0.43 [0.19, 0.96], 0.0396		0.43 [0.25, 0.76], 0.0035	
OR [95%-CI]; p-value	0.35 [0.13, 0.94], 0.0330		0.35 [0.13, 0.95], 0.0341		0.35 [0.17, 0.71], 0.0028	
RD [95%-CI]; p-value	-0.17 [-0.34, -0.00], 0.0467		-0.16 [-0.31, -0.00], 0.0434		-0.17 [-0.28, -0.05], 0.0048	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.7633		0.0722		0.2939	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	7/36 (19.4)	13/77 (16.9)	1/29 (3.4)	19/150 (12.7)	8/65 (12.3)
RR [95%-CI]; p-value	0.42 [0.15, 1.17], 0.0963		4.90 [0.67, 35.77], 0.1175		1.03 [0.48, 2.23], 0.9419	
OR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0890		5.69 [0.71, 45.61], 0.0686		1.03 [0.43, 2.50], 0.9418	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.03], 0.1261		0.13 [0.03, 0.24], 0.0137		0.00 [-0.09, 0.10], 0.9416	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	7/67 (10.4)	7/43 (16.3)	13/135 (9.6)	13/79 (16.5)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.24, 1.70], 0.3727		0.59 [0.29, 1.20], 0.1429	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.60 [0.19, 1.85], 0.3706		0.54 [0.24, 1.23], 0.1402	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.06 [-0.19, 0.07], 0.3882		-0.07 [-0.16, 0.03], 0.1622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7911		0.5869		0.9653	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	9/77 (11.7)	2/29 (6.9)	19/150 (12.7)	9/65 (13.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		1.69 [0.39, 7.38], 0.4822		0.91 [0.44, 1.91], 0.8130	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		1.79 [0.36, 8.81], 0.4708		0.90 [0.38, 2.12], 0.8134	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		0.05 [-0.07, 0.16], 0.4216		-0.01 [-0.11, 0.09], 0.8161	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	8/67 (11.9)	5/43 (11.6)	16/135 (11.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		1.03 [0.36, 2.93], 0.9605		0.94 [0.45, 1.96], 0.8615	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		1.03 [0.31, 3.39], 0.9605		0.93 [0.40, 2.16], 0.8617	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		0.00 [-0.12, 0.13], 0.9604		-0.01 [-0.10, 0.08], 0.8627	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.1437		0.3849		0.0542	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	1/36 (2.8)	10/77 (13.0)	2/29 (6.9)	14/150 (9.3)	3/65 (4.6)
RR [95%-CI]; p-value	1.97 [0.23, 17.01], 0.5366		1.88 [0.44, 8.08], 0.3945		2.02 [0.60, 6.80], 0.2550	
OR [95%-CI]; p-value	2.03 [0.22, 18.85], 0.5260		2.01 [0.41, 9.81], 0.3776		2.13 [0.59, 7.67], 0.2390	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.4795		0.06 [-0.06, 0.18], 0.3155		0.05 [-0.02, 0.12], 0.1806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	5/68 (7.4)	8/36 (22.2)	5/67 (7.5)	4/43 (9.3)	10/135 (7.4)	12/79 (15.2)
RR [95%-CI]; p-value	0.33 [0.12, 0.94], 0.0375		0.80 [0.23, 2.82], 0.7313		0.49 [0.22, 1.08], 0.0755	
OR [95%-CI]; p-value	0.28 [0.08, 0.92], 0.0292		0.79 [0.20, 3.11], 0.7312		0.45 [0.18, 1.09], 0.0704	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0509		-0.02 [-0.13, 0.09], 0.7367		-0.08 [-0.17, 0.01], 0.0924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.1.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9813		0.3475		0.5539	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	7/73 (9.6)	4/36 (11.1)	7/77 (9.1)	2/29 (6.9)	14/150 (9.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.86 [0.27, 2.76], 0.8037		1.32 [0.29, 5.98], 0.7203		1.01 [0.41, 2.51], 0.9810	
OR [95%-CI]; p-value	0.85 [0.23, 3.11], 0.8040		1.35 [0.26, 6.91], 0.7179		1.01 [0.37, 2.76], 0.9810	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8082		0.02 [-0.09, 0.13], 0.7019		0.00 [-0.08, 0.09], 0.9810	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	4/67 (6.0)	5/43 (11.6)	12/135 (8.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		0.51 [0.15, 1.81], 0.2989		0.70 [0.32, 1.55], 0.3816	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		0.48 [0.12, 1.91], 0.2908		0.67 [0.28, 1.64], 0.3809	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		-0.06 [-0.17, 0.05], 0.3193		-0.04 [-0.13, 0.05], 0.3992	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_1_m_soc_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.3.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4447		0.8054		0.4238	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	2/73 (2.7)	6/36 (16.7)	3/77 (3.9)	0/29 (0.0)	5/150 (3.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.16 [0.03, 0.77], 0.0224		2.30 [0.12, 44.52], 0.5820		0.36 [0.11, 1.14], 0.0827	
OR [95%-CI]; p-value	0.14 [0.03, 0.74], 0.0087		2.35 [0.11, 48.40], 0.5685		0.34 [0.10, 1.15], 0.0715	
RD [95%-CI]; p-value	-0.14 [-0.27, -0.01], 0.0321		0.02 [-0.04, 0.09], 0.4972		-0.06 [-0.13, 0.02], 0.1283	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	6/36 (16.7)	3/67 (4.5)	0/43 (0.0)	7/135 (5.2)	6/79 (7.6)
RR [95%-CI]; p-value	0.35 [0.11, 1.17], 0.0887		3.90 [0.20, 75.89], 0.3694		0.68 [0.24, 1.96], 0.4781	
OR [95%-CI]; p-value	0.31 [0.08, 1.19], 0.0759		4.03 [0.20, 82.50], 0.3291		0.67 [0.22, 2.05], 0.4764	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1146		0.03 [-0.03, 0.09], 0.2671		-0.02 [-0.09, 0.05], 0.4959	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_3_m_pt_ae10pct_wt.sas using SAS 9.4

Table 12.4.4.1.3.s3
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0825		0.8341		0.3071	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	4/36 (11.1)	2/77 (2.6)	0/29 (0.0)	8/150 (5.3)	4/65 (6.2)
RR [95%-CI]; p-value	0.74 [0.22, 2.46], 0.6226		1.53 [0.07, 33.00], 0.7852		0.87 [0.27, 2.78], 0.8097	
OR [95%-CI]; p-value	0.72 [0.19, 2.72], 0.6228		1.55 [0.07, 35.32], 0.7831		0.86 [0.25, 2.96], 0.8098	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.09], 0.6379		0.01 [-0.05, 0.07], 0.7627		-0.01 [-0.08, 0.06], 0.8147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	1/68 (1.5)	6/36 (16.7)	5/67 (7.5)	3/43 (7.0)	6/135 (4.4)	9/79 (11.4)
RR [95%-CI]; p-value	0.09 [0.01, 0.70], 0.0220		1.07 [0.27, 4.25], 0.9238		0.39 [0.14, 1.06], 0.0637	
OR [95%-CI]; p-value	0.07 [0.01, 0.65], 0.0033		1.08 [0.24, 4.75], 0.9237		0.36 [0.12, 1.06], 0.0547	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.03], 0.0172		0.00 [-0.09, 0.10], 0.9232		-0.07 [-0.15, 0.01], 0.0817	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_3_m_pt_ae10pct_wt.sas using SAS 9.4

Table 12.4.8.1.1.s3
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9364		0.9529		0.6861	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	3/73 (4.1)	1/36 (2.8)	1/77 (1.3)	0/29 (0.0)	4/150 (2.7)	1/65 (1.5)
RR [95%-CI]; p-value	1.48 [0.16, 13.73], 0.7304		0.77 [0.03, 22.24], 0.8769		1.73 [0.20, 15.21], 0.6196	
OR [95%-CI]; p-value	1.50 [0.15, 14.95], 0.7280		0.76 [0.02, 23.37], 0.8766		1.75 [0.19, 16.00], 0.6142	
RD [95%-CI]; p-value	0.01 [-0.06, 0.08], 0.7108		-0.00 [-0.06, 0.05], 0.8835		0.01 [-0.03, 0.05], 0.5756	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	5/68 (7.4)	2/36 (5.6)	4/67 (6.0)	3/43 (7.0)	9/135 (6.7)	5/79 (6.3)
RR [95%-CI]; p-value	1.32 [0.27, 6.49], 0.7296		0.86 [0.20, 3.64], 0.8329		1.05 [0.37, 3.03], 0.9233	
OR [95%-CI]; p-value	1.35 [0.25, 7.33], 0.7278		0.85 [0.18, 3.98], 0.8329		1.06 [0.34, 3.27], 0.9232	
RD [95%-CI]; p-value	0.02 [-0.08, 0.12], 0.7170		-0.01 [-0.11, 0.08], 0.8354		0.00 [-0.06, 0.07], 0.9227	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_8_1_1_m_soc_sae5pct_wt.sas using SAS 9.4

Table 12.4.8.1.2.s3
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_8_1_2_m_pt_sae5pct_wt.sas using SAS 9.4

Table 12.4.5.1.1.s3
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_5_1_1_m_soc_aeg35pct_wt.sas using SAS 9.4

Table 12.4.5.1.2.s3
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_5_1_2_m_pt_aeg35pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6190		0.7629		0.6433	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	3/36 (8.3)	5/77 (6.5)	1/29 (3.4)	10/150 (6.7)	4/65 (6.2)
RR [95%-CI]; p-value	0.82 [0.21, 3.25], 0.7798		1.88 [0.23, 15.44], 0.5555		1.08 [0.35, 3.33], 0.8888	
OR [95%-CI]; p-value	0.81 [0.18, 3.59], 0.7799		1.94 [0.22, 17.39], 0.5453		1.09 [0.33, 3.61], 0.8887	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.09], 0.7863		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.07, 0.08], 0.8870	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	6/67 (9.0)	3/43 (7.0)	12/135 (8.9)	9/79 (11.4)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		1.28 [0.34, 4.86], 0.7133		0.78 [0.34, 1.77], 0.5524	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		1.31 [0.31, 5.55], 0.7118		0.76 [0.30, 1.89], 0.5525	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		0.02 [-0.08, 0.12], 0.7047		-0.03 [-0.11, 0.06], 0.5634	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.1702		0.9337		0.6054	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	18/73 (24.7)	9/36 (25.0)	11/77 (14.3)	2/29 (6.9)	29/150 (19.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.99 [0.49, 1.97], 0.9689		2.07 [0.49, 8.79], 0.3232		1.14 [0.61, 2.15], 0.6787	
OR [95%-CI]; p-value	0.98 [0.39, 2.47], 0.9689		2.25 [0.47, 10.83], 0.3012		1.18 [0.55, 2.53], 0.6766	
RD [95%-CI]; p-value	-0.00 [-0.18, 0.17], 0.9690		0.07 [-0.05, 0.19], 0.2309		0.02 [-0.09, 0.14], 0.6702	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	10/68 (14.7)	11/36 (30.6)	15/67 (22.4)	5/43 (11.6)	25/135 (18.5)	16/79 (20.3)
RR [95%-CI]; p-value	0.48 [0.23, 1.02], 0.0577		1.93 [0.75, 4.91], 0.1705		0.91 [0.52, 1.61], 0.7551	
OR [95%-CI]; p-value	0.39 [0.15, 1.04], 0.0554		2.19 [0.73, 6.55], 0.1534		0.89 [0.44, 1.80], 0.7557	
RD [95%-CI]; p-value	-0.16 [-0.33, 0.01], 0.0716		0.11 [-0.03, 0.25], 0.1274		-0.02 [-0.13, 0.09], 0.7577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7893		0.6563		0.8313	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	7/77 (9.1)	4/29 (13.8)	17/150 (11.3)	11/65 (16.9)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		0.66 [0.21, 2.09], 0.4781		0.67 [0.33, 1.35], 0.2618	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		0.63 [0.17, 2.32], 0.4791		0.63 [0.28, 1.43], 0.2634	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		-0.05 [-0.19, 0.09], 0.5133		-0.06 [-0.16, 0.05], 0.2936	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	8/36 (22.2)	10/67 (14.9)	7/43 (16.3)	19/135 (14.1)	15/79 (19.0)
RR [95%-CI]; p-value	0.60 [0.25, 1.41], 0.2389		0.92 [0.38, 2.23], 0.8478		0.74 [0.40, 1.37], 0.3418	
OR [95%-CI]; p-value	0.53 [0.19, 1.53], 0.2384		0.90 [0.32, 2.58], 0.8480		0.70 [0.33, 1.47], 0.3427	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2646		-0.01 [-0.15, 0.13], 0.8491		-0.05 [-0.15, 0.06], 0.3568	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.4851		0.7103		0.8532	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	19/73 (26.0)	8/36 (22.2)	15/77 (19.5)	6/29 (20.7)	34/150 (22.7)	14/65 (21.5)
RR [95%-CI]; p-value	1.17 [0.57, 2.41], 0.6684		0.94 [0.40, 2.19], 0.8889		1.05 [0.61, 1.82], 0.8557	
OR [95%-CI]; p-value	1.23 [0.48, 3.16], 0.6651		0.93 [0.32, 2.68], 0.8893		1.07 [0.53, 2.16], 0.8552	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6591		-0.01 [-0.18, 0.16], 0.8904		0.01 [-0.11, 0.13], 0.8542	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	19/68 (27.9)	12/36 (33.3)	18/67 (26.9)	10/43 (23.3)	37/135 (27.4)	22/79 (27.8)
RR [95%-CI]; p-value	0.84 [0.46, 1.53], 0.5639		1.16 [0.59, 2.26], 0.6736		0.98 [0.63, 1.54], 0.9445	
OR [95%-CI]; p-value	0.78 [0.32, 1.86], 0.5674		1.21 [0.50, 2.95], 0.6715		0.98 [0.53, 1.82], 0.9445	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.13], 0.5726		0.04 [-0.13, 0.20], 0.6680		-0.00 [-0.13, 0.12], 0.9446	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.9043		0.4341		0.5118	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	3/36 (8.3)	6/77 (7.8)	2/29 (6.9)	16/150 (10.7)	5/65 (7.7)
RR [95%-CI]; p-value	1.64 [0.48, 5.61], 0.4272		1.13 [0.24, 5.28], 0.8767		1.39 [0.53, 3.63], 0.5050	
OR [95%-CI]; p-value	1.75 [0.45, 6.78], 0.4163		1.14 [0.22, 6.00], 0.8763		1.43 [0.50, 4.09], 0.4999	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3804		0.01 [-0.10, 0.12], 0.8732		0.03 [-0.05, 0.11], 0.4742	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	2/36 (5.6)	5/67 (7.5)	1/43 (2.3)	12/135 (8.9)	3/79 (3.8)
RR [95%-CI]; p-value	1.85 [0.41, 8.46], 0.4260		3.21 [0.39, 26.54], 0.2794		2.34 [0.68, 8.04], 0.1769	
OR [95%-CI]; p-value	1.95 [0.38, 9.92], 0.4135		3.39 [0.38, 30.04], 0.2470		2.47 [0.68, 9.04], 0.1592	
RD [95%-CI]; p-value	0.05 [-0.06, 0.15], 0.3718		0.05 [-0.03, 0.13], 0.1932		0.05 [-0.01, 0.11], 0.1183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2208		0.4662		0.1763	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	11/73 (15.1)	4/36 (11.1)	10/77 (13.0)	3/29 (10.3)	21/150 (14.0)	7/65 (10.8)
RR [95%-CI]; p-value	1.36 [0.46, 3.96], 0.5777		1.26 [0.37, 4.24], 0.7142		1.30 [0.58, 2.91], 0.5226	
OR [95%-CI]; p-value	1.42 [0.42, 4.81], 0.5727		1.29 [0.33, 5.08], 0.7116		1.35 [0.54, 3.35], 0.5180	
RD [95%-CI]; p-value	0.04 [-0.09, 0.17], 0.5551		0.03 [-0.11, 0.16], 0.6989		0.03 [-0.06, 0.13], 0.4988	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	4/67 (6.0)	4/43 (9.3)	10/135 (7.4)	10/79 (12.7)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.17, 2.43], 0.5140		0.59 [0.25, 1.34], 0.2065	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.62 [0.15, 2.62], 0.5114		0.55 [0.22, 1.39], 0.2028	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.03 [-0.14, 0.07], 0.5289		-0.05 [-0.14, 0.03], 0.2293	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.8092		0.7112		0.9625	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	16/73 (21.9)	11/36 (30.6)	10/77 (13.0)	3/29 (10.3)	26/150 (17.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.72 [0.37, 1.38], 0.3207		1.26 [0.37, 4.24], 0.7142		0.80 [0.45, 1.44], 0.4636	
OR [95%-CI]; p-value	0.64 [0.26, 1.57], 0.3258		1.29 [0.33, 5.08], 0.7116		0.76 [0.37, 1.58], 0.4668	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3413		0.03 [-0.11, 0.16], 0.6989		-0.04 [-0.16, 0.07], 0.4806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	12/68 (17.6)	10/36 (27.8)	15/67 (22.4)	10/43 (23.3)	27/135 (20.0)	20/79 (25.3)
RR [95%-CI]; p-value	0.64 [0.30, 1.33], 0.2267		0.96 [0.48, 1.94], 0.9155		0.79 [0.48, 1.31], 0.3624	
OR [95%-CI]; p-value	0.56 [0.21, 1.45], 0.2288		0.95 [0.38, 2.37], 0.9156		0.74 [0.38, 1.43], 0.3646	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.07], 0.2486		-0.01 [-0.17, 0.15], 0.9158		-0.05 [-0.17, 0.06], 0.3741	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4955		0.0291		0.0732	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	15/73 (20.5)	12/36 (33.3)	14/77 (18.2)	2/29 (6.9)	29/150 (19.3)	14/65 (21.5)
RR [95%-CI]; p-value	0.62 [0.32, 1.18], 0.1419		2.64 [0.64, 10.89], 0.1805		0.90 [0.51, 1.58], 0.7092	
OR [95%-CI]; p-value	0.52 [0.21, 1.27], 0.1459		3.00 [0.64, 14.12], 0.1479		0.87 [0.43, 1.79], 0.7105	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1632		0.11 [-0.01, 0.24], 0.0797		-0.02 [-0.14, 0.10], 0.7147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	9/68 (13.2)	11/36 (30.6)	8/67 (11.9)	12/43 (27.9)	17/135 (12.6)	23/79 (29.1)
RR [95%-CI]; p-value	0.43 [0.20, 0.95], 0.0362		0.43 [0.19, 0.96], 0.0396		0.43 [0.25, 0.76], 0.0035	
OR [95%-CI]; p-value	0.35 [0.13, 0.94], 0.0330		0.35 [0.13, 0.95], 0.0341		0.35 [0.17, 0.71], 0.0028	
RD [95%-CI]; p-value	-0.17 [-0.34, -0.00], 0.0467		-0.16 [-0.31, -0.00], 0.0434		-0.17 [-0.28, -0.05], 0.0048	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.7633		0.0722		0.2939	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	7/36 (19.4)	13/77 (16.9)	1/29 (3.4)	19/150 (12.7)	8/65 (12.3)
RR [95%-CI]; p-value	0.42 [0.15, 1.17], 0.0963		4.90 [0.67, 35.77], 0.1175		1.03 [0.48, 2.23], 0.9419	
OR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0890		5.69 [0.71, 45.61], 0.0686		1.03 [0.43, 2.50], 0.9418	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.03], 0.1261		0.13 [0.03, 0.24], 0.0137		0.00 [-0.09, 0.10], 0.9416	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	6/36 (16.7)	7/67 (10.4)	7/43 (16.3)	13/135 (9.6)	13/79 (16.5)
RR [95%-CI]; p-value	0.53 [0.18, 1.52], 0.2383		0.64 [0.24, 1.70], 0.3727		0.59 [0.29, 1.20], 0.1429	
OR [95%-CI]; p-value	0.48 [0.14, 1.63], 0.2336		0.60 [0.19, 1.85], 0.3706		0.54 [0.24, 1.23], 0.1402	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2693		-0.06 [-0.19, 0.07], 0.3882		-0.07 [-0.16, 0.03], 0.1622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.3783		0.6938		0.3435	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	9/73 (12.3)	3/36 (8.3)	6/77 (7.8)	2/29 (6.9)	15/150 (10.0)	5/65 (7.7)
RR [95%-CI]; p-value	1.48 [0.43, 5.13], 0.5372		1.13 [0.24, 5.28], 0.8767		1.30 [0.49, 3.43], 0.5958	
OR [95%-CI]; p-value	1.55 [0.39, 6.10], 0.5308		1.14 [0.22, 6.00], 0.8763		1.33 [0.46, 3.84], 0.5926	
RD [95%-CI]; p-value	0.04 [-0.08, 0.16], 0.5056		0.01 [-0.10, 0.12], 0.8732		0.02 [-0.06, 0.10], 0.5748	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	2/36 (5.6)	6/67 (9.0)	5/43 (11.6)	8/135 (5.9)	7/79 (8.9)
RR [95%-CI]; p-value	0.53 [0.08, 3.60], 0.5157		0.77 [0.25, 2.37], 0.6486		0.67 [0.25, 1.77], 0.4190	
OR [95%-CI]; p-value	0.52 [0.07, 3.82], 0.5095		0.75 [0.21, 2.62], 0.6484		0.65 [0.23, 1.86], 0.4171	
RD [95%-CI]; p-value	-0.03 [-0.11, 0.06], 0.5462		-0.03 [-0.14, 0.09], 0.6563		-0.03 [-0.10, 0.04], 0.4385	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7911		0.5869		0.9653	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	7/36 (19.4)	9/77 (11.7)	2/29 (6.9)	19/150 (12.7)	9/65 (13.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.70], 0.4351		1.69 [0.39, 7.38], 0.4822		0.91 [0.44, 1.91], 0.8130	
OR [95%-CI]; p-value	0.66 [0.23, 1.90], 0.4368		1.79 [0.36, 8.81], 0.4708		0.90 [0.38, 2.12], 0.8134	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4571		0.05 [-0.07, 0.16], 0.4216		-0.01 [-0.11, 0.09], 0.8161	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	8/67 (11.9)	5/43 (11.6)	16/135 (11.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		1.03 [0.36, 2.93], 0.9605		0.94 [0.45, 1.96], 0.8615	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		1.03 [0.31, 3.39], 0.9605		0.93 [0.40, 2.16], 0.8617	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		0.00 [-0.12, 0.13], 0.9604		-0.01 [-0.10, 0.08], 0.8627	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.1437		0.3849		0.0542	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	1/36 (2.8)	10/77 (13.0)	2/29 (6.9)	14/150 (9.3)	3/65 (4.6)
RR [95%-CI]; p-value	1.97 [0.23, 17.01], 0.5366		1.88 [0.44, 8.08], 0.3945		2.02 [0.60, 6.80], 0.2550	
OR [95%-CI]; p-value	2.03 [0.22, 18.85], 0.5260		2.01 [0.41, 9.81], 0.3776		2.13 [0.59, 7.67], 0.2390	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.4795		0.06 [-0.06, 0.18], 0.3155		0.05 [-0.02, 0.12], 0.1806	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	5/68 (7.4)	8/36 (22.2)	5/67 (7.5)	4/43 (9.3)	10/135 (7.4)	12/79 (15.2)
RR [95%-CI]; p-value	0.33 [0.12, 0.94], 0.0375		0.80 [0.23, 2.82], 0.7313		0.49 [0.22, 1.08], 0.0755	
OR [95%-CI]; p-value	0.28 [0.08, 0.92], 0.0292		0.79 [0.20, 3.11], 0.7312		0.45 [0.18, 1.09], 0.0704	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0509		-0.02 [-0.13, 0.09], 0.7367		-0.08 [-0.17, 0.01], 0.0924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.2.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9813		0.3475		0.5539	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	7/73 (9.6)	4/36 (11.1)	7/77 (9.1)	2/29 (6.9)	14/150 (9.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.86 [0.27, 2.76], 0.8037		1.32 [0.29, 5.98], 0.7203		1.01 [0.41, 2.51], 0.9810	
OR [95%-CI]; p-value	0.85 [0.23, 3.11], 0.8040		1.35 [0.26, 6.91], 0.7179		1.01 [0.37, 2.76], 0.9810	
RD [95%-CI]; p-value	-0.02 [-0.14, 0.11], 0.8082		0.02 [-0.09, 0.13], 0.7019		0.00 [-0.08, 0.09], 0.9810	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	8/68 (11.8)	5/36 (13.9)	4/67 (6.0)	5/43 (11.6)	12/135 (8.9)	10/79 (12.7)
RR [95%-CI]; p-value	0.85 [0.30, 2.40], 0.7548		0.51 [0.15, 1.81], 0.2989		0.70 [0.32, 1.55], 0.3816	
OR [95%-CI]; p-value	0.83 [0.25, 2.74], 0.7553		0.48 [0.12, 1.91], 0.2908		0.67 [0.28, 1.64], 0.3809	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.7603		-0.06 [-0.17, 0.05], 0.3193		-0.04 [-0.13, 0.05], 0.3992	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_2_m_soc_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.4.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4447		0.8054		0.4238	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	2/73 (2.7)	6/36 (16.7)	3/77 (3.9)	0/29 (0.0)	5/150 (3.3)	6/65 (9.2)
RR [95%-CI]; p-value	0.16 [0.03, 0.77], 0.0224		2.30 [0.12, 44.52], 0.5820		0.36 [0.11, 1.14], 0.0827	
OR [95%-CI]; p-value	0.14 [0.03, 0.74], 0.0087		2.35 [0.11, 48.40], 0.5685		0.34 [0.10, 1.15], 0.0715	
RD [95%-CI]; p-value	-0.14 [-0.27, -0.01], 0.0321		0.02 [-0.04, 0.09], 0.4972		-0.06 [-0.13, 0.02], 0.1283	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	6/36 (16.7)	3/67 (4.5)	0/43 (0.0)	7/135 (5.2)	6/79 (7.6)
RR [95%-CI]; p-value	0.35 [0.11, 1.17], 0.0887		3.90 [0.20, 75.89], 0.3694		0.68 [0.24, 1.96], 0.4781	
OR [95%-CI]; p-value	0.31 [0.08, 1.19], 0.0759		4.03 [0.20, 82.50], 0.3291		0.67 [0.22, 2.05], 0.4764	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1146		0.03 [-0.03, 0.09], 0.2671		-0.02 [-0.09, 0.05], 0.4959	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_4_m_pt_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.4.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.0825		0.8341		0.3071	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	6/73 (8.2)	4/36 (11.1)	2/77 (2.6)	0/29 (0.0)	8/150 (5.3)	4/65 (6.2)
RR [95%-CI]; p-value	0.74 [0.22, 2.46], 0.6226		1.53 [0.07, 33.00], 0.7852		0.87 [0.27, 2.78], 0.8097	
OR [95%-CI]; p-value	0.72 [0.19, 2.72], 0.6228		1.55 [0.07, 35.32], 0.7831		0.86 [0.25, 2.96], 0.8098	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.09], 0.6379		0.01 [-0.05, 0.07], 0.7627		-0.01 [-0.08, 0.06], 0.8147	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	1/68 (1.5)	6/36 (16.7)	5/67 (7.5)	3/43 (7.0)	6/135 (4.4)	9/79 (11.4)
RR [95%-CI]; p-value	0.09 [0.01, 0.70], 0.0220		1.07 [0.27, 4.25], 0.9238		0.39 [0.14, 1.06], 0.0637	
OR [95%-CI]; p-value	0.07 [0.01, 0.65], 0.0033		1.08 [0.24, 4.75], 0.9237		0.36 [0.12, 1.06], 0.0547	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.03], 0.0172		0.00 [-0.09, 0.10], 0.9232		-0.07 [-0.15, 0.01], 0.0817	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_4_m_pt_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.4.s3
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.9476		0.2163		0.3945	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	4/73 (5.5)	2/36 (5.6)	5/77 (6.5)	1/29 (3.4)	9/150 (6.0)	3/65 (4.6)
RR [95%-CI]; p-value	0.99 [0.19, 5.13], 0.9869		1.88 [0.23, 15.44], 0.5555		1.30 [0.36, 4.65], 0.6864	
OR [95%-CI]; p-value	0.99 [0.17, 5.65], 0.9869		1.94 [0.22, 17.39], 0.5453		1.32 [0.35, 5.04], 0.6846	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.09], 0.9870		0.03 [-0.06, 0.12], 0.4889		0.01 [-0.05, 0.08], 0.6696	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	6/68 (8.8)	3/36 (8.3)	3/67 (4.5)	5/43 (11.6)	9/135 (6.7)	8/79 (10.1)
RR [95%-CI]; p-value	1.06 [0.28, 3.99], 0.9327		0.39 [0.10, 1.53], 0.1750		0.66 [0.26, 1.64], 0.3684	
OR [95%-CI]; p-value	1.06 [0.25, 4.53], 0.9326		0.36 [0.08, 1.58], 0.1588		0.63 [0.23, 1.72], 0.3664	
RD [95%-CI]; p-value	0.00 [-0.11, 0.12], 0.9320		-0.07 [-0.18, 0.04], 0.1938		-0.03 [-0.11, 0.04], 0.3890	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_4_m_pt_ae1pct_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.7820		0.5567		0.4248	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	11/73 (15.1)	2/36 (5.6)	5/77 (6.5)	2/29 (6.9)	16/150 (10.7)	4/65 (6.2)
RR [95%-CI]; p-value	2.71 [0.63, 11.60], 0.1783		0.94 [0.19, 4.59], 0.9406		1.73 [0.60, 4.98], 0.3074	
OR [95%-CI]; p-value	3.02 [0.63, 14.41], 0.1495		0.94 [0.17, 5.12], 0.9406		1.82 [0.58, 5.67], 0.2954	
RD [95%-CI]; p-value	0.10 [-0.02, 0.21], 0.0932		-0.00 [-0.11, 0.10], 0.9414		0.05 [-0.03, 0.12], 0.2476	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	4/68 (5.9)	0/36 (0.0)	4/67 (6.0)	5/43 (11.6)	8/135 (5.9)	5/79 (6.3)
RR [95%-CI]; p-value	4.29 [0.23, 79.01], 0.3267		0.51 [0.15, 1.81], 0.2989		0.94 [0.32, 2.76], 0.9051	
OR [95%-CI]; p-value	4.50 [0.23, 87.55], 0.2787		0.48 [0.12, 1.91], 0.2908		0.93 [0.29, 2.95], 0.9051	
RD [95%-CI]; p-value	0.05 [-0.02, 0.11], 0.1898		-0.06 [-0.17, 0.05], 0.3193		-0.00 [-0.07, 0.06], 0.9059	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9767		0.7182		0.6045	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	1/73 (1.4)	0/36 (0.0)	1/77 (1.3)	0/29 (0.0)	2/150 (1.3)	0/65 (0.0)
RR [95%-CI]; p-value	1.00 [0.03, 29.12], 1.0000		0.77 [0.03, 22.24], 0.8769		1.75 [0.08, 38.21], 0.7231	
OR [95%-CI]; p-value	1.00 [0.03, 30.52], 1.0000		0.76 [0.02, 23.37], 0.8766		1.76 [0.08, 39.49], 0.7193	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 1.0000		-0.00 [-0.06, 0.05], 0.8835		0.01 [-0.02, 0.03], 0.6894	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	1/68 (1.5)	0/36 (0.0)	0/67 (0.0)	1/43 (2.3)	1/135 (0.7)	1/79 (1.3)
RR [95%-CI]; p-value	1.07 [0.04, 31.24], 0.9671		0.32 [0.01, 9.29], 0.5062		0.59 [0.04, 9.23], 0.7034	
OR [95%-CI]; p-value	1.07 [0.04, 32.81], 0.9671		0.31 [0.01, 9.55], 0.4827		0.58 [0.04, 9.44], 0.7001	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9667		-0.02 [-0.07, 0.03], 0.5301		-0.01 [-0.03, 0.02], 0.7188	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8743		0.8820		0.6319	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	10/73 (13.7)	2/36 (5.6)	4/77 (5.2)	2/29 (6.9)	14/150 (9.3)	4/65 (6.2)
RR [95%-CI]; p-value	2.47 [0.57, 10.67], 0.2272		0.75 [0.15, 3.89], 0.7353		1.52 [0.52, 4.43], 0.4465	
OR [95%-CI]; p-value	2.70 [0.56, 13.03], 0.2014		0.74 [0.13, 4.27], 0.7354		1.57 [0.50, 4.97], 0.4395	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1421		-0.02 [-0.12, 0.09], 0.7501		0.03 [-0.04, 0.11], 0.4042	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	3/68 (4.4)	0/36 (0.0)	4/67 (6.0)	4/43 (9.3)	7/135 (5.2)	4/79 (5.1)
RR [95%-CI]; p-value	3.22 [0.17, 62.57], 0.4397		0.64 [0.17, 2.43], 0.5140		1.02 [0.31, 3.39], 0.9689	
OR [95%-CI]; p-value	3.32 [0.16, 68.19], 0.4100		0.62 [0.15, 2.62], 0.5114		1.03 [0.29, 3.62], 0.9689	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3337		-0.03 [-0.14, 0.07], 0.5289		0.00 [-0.06, 0.06], 0.9688	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.9420		0.6109		0.8382	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	1/36 (2.8)	3/77 (3.9)	0/29 (0.0)	8/150 (5.3)	1/65 (1.5)
RR [95%-CI]; p-value	2.47 [0.30, 20.33], 0.4018		2.30 [0.12, 44.52], 0.5820		3.47 [0.44, 27.16], 0.2365	
OR [95%-CI]; p-value	2.57 [0.29, 22.89], 0.3807		2.35 [0.11, 48.40], 0.5685		3.61 [0.44, 29.44], 0.2019	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3124		0.02 [-0.04, 0.09], 0.4972		0.04 [-0.01, 0.08], 0.1118	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	0/36 (0.0)	0/67 (0.0)	0/43 (0.0)	2/135 (1.5)	0/79 (0.0)
RR [95%-CI]; p-value	2.15 [0.10, 46.38], 0.6260		NA		2.36 [0.11, 51.59], 0.5864	
OR [95%-CI]; p-value	2.18 [0.10, 49.68], 0.6163		NA		2.38 [0.11, 53.35], 0.5742	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5761		NA		0.01 [-0.02, 0.04], 0.5327	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8268		0.4665		0.5125	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	5/73 (6.8)	4/36 (11.1)	6/77 (7.8)	3/29 (10.3)	11/150 (7.3)	7/65 (10.8)
RR [95%-CI]; p-value	0.62 [0.18, 2.16], 0.4491		0.75 [0.20, 2.82], 0.6736		0.68 [0.28, 1.68], 0.4036	
OR [95%-CI]; p-value	0.59 [0.15, 2.34], 0.4471		0.73 [0.17, 3.14], 0.6743		0.66 [0.24, 1.78], 0.4035	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.08], 0.4786		-0.03 [-0.15, 0.10], 0.6913		-0.03 [-0.12, 0.05], 0.4343	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	5/36 (13.9)	7/67 (10.4)	3/43 (7.0)	14/135 (10.4)	8/79 (10.1)
RR [95%-CI]; p-value	0.74 [0.25, 2.17], 0.5847		1.50 [0.41, 5.48], 0.5418		1.02 [0.45, 2.33], 0.9548	
OR [95%-CI]; p-value	0.71 [0.21, 2.43], 0.5851		1.56 [0.38, 6.37], 0.5366		1.03 [0.41, 2.57], 0.9548	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.10], 0.5993		0.03 [-0.07, 0.14], 0.5196		0.00 [-0.08, 0.09], 0.9547	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.6016		0.5316		0.8734	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	2/73 (2.7)	0/36 (0.0)	2/77 (2.6)	1/29 (3.4)	4/150 (2.7)	1/65 (1.5)
RR [95%-CI]; p-value	2.00 [0.09, 43.23], 0.6585		0.75 [0.07, 7.99], 0.8141		1.73 [0.20, 15.21], 0.6196	
OR [95%-CI]; p-value	2.03 [0.09, 46.15], 0.6510		0.75 [0.07, 8.56], 0.8138		1.75 [0.19, 16.00], 0.6142	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.6134		-0.01 [-0.08, 0.07], 0.8248		0.01 [-0.03, 0.05], 0.5756	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	0/68 (0.0)	0/36 (0.0)	2/67 (3.0)	0/43 (0.0)	2/135 (1.5)	0/79 (0.0)
RR [95%-CI]; p-value	NA		2.60 [0.12, 56.25], 0.5430		2.36 [0.11, 51.59], 0.5864	
OR [95%-CI]; p-value	NA		2.65 [0.12, 60.10], 0.5261		2.38 [0.11, 53.35], 0.5742	
RD [95%-CI]; p-value	NA		0.02 [-0.03, 0.07], 0.4857		0.01 [-0.02, 0.04], 0.5327	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.4488		0.3474		0.2390	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	3/73 (4.1)	4/36 (11.1)	4/77 (5.2)	3/29 (10.3)	7/150 (4.7)	7/65 (10.8)
RR [95%-CI]; p-value	0.37 [0.09, 1.57], 0.1766		0.50 [0.12, 2.11], 0.3467		0.43 [0.16, 1.19], 0.1034	
OR [95%-CI]; p-value	0.34 [0.07, 1.62], 0.1608		0.47 [0.10, 2.27], 0.3412		0.41 [0.14, 1.21], 0.0958	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2217		-0.05 [-0.17, 0.07], 0.4058		-0.06 [-0.14, 0.02], 0.1475	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	7/68 (10.3)	5/36 (13.9)	6/67 (9.0)	3/43 (7.0)	13/135 (9.6)	8/79 (10.1)
RR [95%-CI]; p-value	0.74 [0.25, 2.17], 0.5847		1.28 [0.34, 4.86], 0.7133		0.95 [0.41, 2.19], 0.9061	
OR [95%-CI]; p-value	0.71 [0.21, 2.43], 0.5851		1.31 [0.31, 5.55], 0.7118		0.95 [0.37, 2.39], 0.9061	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.10], 0.5993		0.02 [-0.08, 0.12], 0.7047		-0.00 [-0.09, 0.08], 0.9067	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.7.s3
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8780		0.6673		0.7463	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	3/73 (4.1)	0/36 (0.0)	3/77 (3.9)	1/29 (3.4)	6/150 (4.0)	1/65 (1.5)
RR [95%-CI]; p-value	3.00 [0.15, 58.32], 0.4681		1.13 [0.12, 10.43], 0.9143		2.60 [0.32, 21.17], 0.3718	
OR [95%-CI]; p-value	3.09 [0.15, 63.28], 0.4423		1.14 [0.11, 11.37], 0.9141		2.67 [0.31, 22.61], 0.3503	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3638		0.00 [-0.07, 0.08], 0.9118		0.02 [-0.02, 0.07], 0.2657	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	2/68 (2.9)	0/36 (0.0)	2/67 (3.0)	0/43 (0.0)	4/135 (3.0)	0/79 (0.0)
RR [95%-CI]; p-value	2.15 [0.10, 46.38], 0.6260		2.60 [0.12, 56.25], 0.5430		4.71 [0.25, 87.95], 0.2993	
OR [95%-CI]; p-value	2.18 [0.10, 49.68], 0.6163		2.65 [0.12, 60.10], 0.5261		4.82 [0.25, 92.47], 0.2493	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5761		0.02 [-0.03, 0.07], 0.4857		0.02 [-0.01, 0.06], 0.1717	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_7_m_pt_smq_wt.sas using SAS 9.4

Table 12.4.4.1.6.s3
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.3308		0.8647		0.7277	
1.Baseline Weight < 94.25 Kg	N1=73	N1=36	N1=77	N1=29	N1=150	N1=65
n/N1 (%)	13/73 (17.8)	7/36 (19.4)	12/77 (15.6)	3/29 (10.3)	25/150 (16.7)	10/65 (15.4)
RR [95%-CI]; p-value	0.92 [0.40, 2.10], 0.8351		1.51 [0.46, 4.96], 0.5000		1.08 [0.55, 2.12], 0.8157	
OR [95%-CI]; p-value	0.90 [0.32, 2.49], 0.8356		1.60 [0.42, 6.14], 0.4902		1.10 [0.49, 2.45], 0.8151	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8374		0.05 [-0.08, 0.19], 0.4545		0.01 [-0.09, 0.12], 0.8127	
2.Baseline Weight≥ 94.25 Kg	N2=68	N2=36	N2=67	N2=43	N2=135	N2=79
n/N2 (%)	11/68 (16.2)	11/36 (30.6)	16/67 (23.9)	6/43 (14.0)	27/135 (20.0)	17/79 (21.5)
RR [95%-CI]; p-value	0.53 [0.25, 1.10], 0.0884		1.71 [0.73, 4.03], 0.2189		0.93 [0.54, 1.59], 0.7903	
OR [95%-CI]; p-value	0.44 [0.17, 1.14], 0.0876		1.93 [0.69, 5.42], 0.2040		0.91 [0.46, 1.80], 0.7908	
RD [95%-CI]; p-value	-0.14 [-0.32, 0.03], 0.1055		0.10 [-0.05, 0.24], 0.1809		-0.02 [-0.13, 0.10], 0.7922	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt/T12_4_4_1_6_m_pt_adr_wt.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.0911		0.6196		0.1952	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	61/85 (71.8)	34/48 (70.8)	66/98 (67.3)	29/46 (63.0)	127/183 (69.4)	63/94 (67.0)
RR [95%-CI]; p-value	1.01 [0.81, 1.27], 0.9095		1.07 [0.82, 1.39], 0.6196		1.04 [0.87, 1.23], 0.6901	
OR [95%-CI]; p-value	1.05 [0.48, 2.29], 0.9091		1.21 [0.58, 2.52], 0.6113		1.12 [0.66, 1.90], 0.6864	
RD [95%-CI]; p-value	0.01 [-0.15, 0.17], 0.9093		0.04 [-0.12, 0.21], 0.6147		0.02 [-0.09, 0.14], 0.6883	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	40/56 (71.4)	22/24 (91.7)	25/46 (54.3)	15/26 (57.7)	65/102 (63.7)	37/50 (74.0)
RR [95%-CI]; p-value	0.78 [0.63, 0.96], 0.0170		0.94 [0.62, 1.44], 0.7817		0.86 [0.69, 1.07], 0.1831	
OR [95%-CI]; p-value	0.23 [0.05, 1.08], 0.0470		0.87 [0.33, 2.30], 0.7838		0.62 [0.29, 1.31], 0.2053	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0143		-0.03 [-0.27, 0.20], 0.7832		-0.10 [-0.26, 0.05], 0.1889	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.9004		0.3586		0.2466	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	11/85 (12.9)	8/48 (16.7)	10/98 (10.2)	2/46 (4.3)	21/183 (11.5)	10/94 (10.6)
RR [95%-CI]; p-value	0.78 [0.34, 1.80], 0.5546		2.35 [0.54, 10.28], 0.2577		1.08 [0.53, 2.20], 0.8346	
OR [95%-CI]; p-value	0.74 [0.28, 2.00], 0.5554		2.50 [0.52, 11.91], 0.2358		1.09 [0.49, 2.42], 0.8343	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.09], 0.5663		0.06 [-0.03, 0.14], 0.1721		0.01 [-0.07, 0.09], 0.8325	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	6/56 (10.7)	3/24 (12.5)	9/46 (19.6)	0/26 (0.0)	15/102 (14.7)	3/50 (6.0)
RR [95%-CI]; p-value	0.86 [0.23, 3.15], 0.8163		10.37 [0.63, 171.78], 0.1025		2.45 [0.74, 8.08], 0.1406	
OR [95%-CI]; p-value	0.84 [0.19, 3.68], 0.8168		12.65 [0.70, 227.95], 0.0317		2.70 [0.74, 9.81], 0.1186	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8215		0.18 [0.05, 0.30], 0.0059		0.09 [-0.01, 0.18], 0.0730	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.8363		0.6160		0.6665	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	4/48 (8.3)	5/98 (5.1)	4/46 (8.7)	15/183 (8.2)	8/94 (8.5)
RR [95%-CI]; p-value	1.41 [0.47, 4.26], 0.5405		0.59 [0.17, 2.08], 0.4096		0.96 [0.42, 2.19], 0.9285	
OR [95%-CI]; p-value	1.47 [0.43, 4.96], 0.5357		0.56 [0.14, 2.21], 0.4062		0.96 [0.39, 2.35], 0.9286	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5176		-0.04 [-0.13, 0.06], 0.4456		-0.00 [-0.07, 0.07], 0.9290	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	2/24 (8.3)	5/46 (10.9)	3/26 (11.5)	13/102 (12.7)	5/50 (10.0)
RR [95%-CI]; p-value	1.71 [0.39, 7.48], 0.4735		0.94 [0.24, 3.63], 0.9308		1.27 [0.48, 3.38], 0.6256	
OR [95%-CI]; p-value	1.83 [0.36, 9.35], 0.4607		0.93 [0.20, 4.27], 0.9309		1.31 [0.44, 3.92], 0.6226	
RD [95%-CI]; p-value	0.06 [-0.08, 0.20], 0.4166		-0.01 [-0.16, 0.15], 0.9314		0.03 [-0.08, 0.13], 0.6096	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.5806		0.5890		0.9904	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	18/85 (21.2)	7/48 (14.6)	13/98 (13.3)	7/46 (15.2)	31/183 (16.9)	14/94 (14.9)
RR [95%-CI]; p-value	1.45 [0.65, 3.23], 0.3597		0.87 [0.37, 2.04], 0.7514		1.14 [0.64, 2.03], 0.6636	
OR [95%-CI]; p-value	1.57 [0.61, 4.09], 0.3499		0.85 [0.32, 2.30], 0.7521		1.17 [0.59, 2.32], 0.6620	
RD [95%-CI]; p-value	0.07 [-0.07, 0.20], 0.3288		-0.02 [-0.14, 0.10], 0.7570		0.02 [-0.07, 0.11], 0.6565	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	12/56 (21.4)	5/24 (20.8)	9/46 (19.6)	4/26 (15.4)	21/102 (20.6)	9/50 (18.0)
RR [95%-CI]; p-value	1.03 [0.41, 2.60], 0.9525		1.27 [0.43, 3.73], 0.6612		1.14 [0.57, 2.31], 0.7083	
OR [95%-CI]; p-value	1.04 [0.32, 3.35], 0.9524		1.34 [0.37, 4.86], 0.6578		1.18 [0.50, 2.81], 0.7064	
RD [95%-CI]; p-value	0.01 [-0.19, 0.20], 0.9522		0.04 [-0.14, 0.22], 0.6488		0.03 [-0.11, 0.16], 0.7013	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.1480		0.2484		0.8388	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	11/85 (12.9)	2/48 (4.2)	7/98 (7.1)	3/46 (6.5)	18/183 (9.8)	5/94 (5.3)
RR [95%-CI]; p-value	3.11 [0.72, 13.43], 0.1293		1.10 [0.30, 4.04], 0.8914		1.85 [0.71, 4.83], 0.2090	
OR [95%-CI]; p-value	3.42 [0.72, 16.12], 0.1017		1.10 [0.27, 4.47], 0.8913		1.94 [0.70, 5.41], 0.1970	
RD [95%-CI]; p-value	0.09 [-0.00, 0.18], 0.0589		0.01 [-0.08, 0.09], 0.8896		0.05 [-0.02, 0.11], 0.1574	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	3/24 (12.5)	8/46 (17.4)	1/26 (3.8)	13/102 (12.7)	4/50 (8.0)
RR [95%-CI]; p-value	0.71 [0.19, 2.75], 0.6250		4.52 [0.60, 34.17], 0.1437		1.59 [0.55, 4.64], 0.3929	
OR [95%-CI]; p-value	0.69 [0.15, 3.13], 0.6256		5.26 [0.62, 44.70], 0.0951		1.68 [0.52, 5.44], 0.3832	
RD [95%-CI]; p-value	-0.04 [-0.19, 0.12], 0.6450		0.14 [0.00, 0.27], 0.0445		0.05 [-0.05, 0.15], 0.3485	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.2030		0.1741		0.8265	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	0/48 (0.0)	3/98 (3.1)	3/46 (6.5)	8/183 (4.4)	3/94 (3.2)
RR [95%-CI]; p-value	5.71 [0.32, 102.22], 0.2369		0.47 [0.10, 2.24], 0.3425		1.37 [0.37, 5.04], 0.6361	
OR [95%-CI]; p-value	6.00 [0.32, 112.26], 0.1750		0.45 [0.09, 2.33], 0.3326		1.39 [0.36, 5.35], 0.6339	
RD [95%-CI]; p-value	0.05 [-0.01, 0.11], 0.0984		-0.03 [-0.11, 0.04], 0.3911		0.01 [-0.03, 0.06], 0.6171	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	3/56 (5.4)	2/24 (8.3)	4/46 (8.7)	0/26 (0.0)	7/102 (6.9)	2/50 (4.0)
RR [95%-CI]; p-value	0.64 [0.11, 3.60], 0.6155		4.61 [0.25, 83.83], 0.3019		1.72 [0.37, 7.96], 0.4905	
OR [95%-CI]; p-value	0.62 [0.10, 3.99], 0.6143		4.95 [0.25, 97.54], 0.2472		1.77 [0.35, 8.84], 0.4823	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.10], 0.6416		0.07 [-0.03, 0.16], 0.1667		0.03 [-0.04, 0.10], 0.4433	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.9033		0.9223		0.7139	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	2/85 (2.4)	1/48 (2.1)	2/98 (2.0)	1/46 (2.2)	4/183 (2.2)	2/94 (2.1)
RR [95%-CI]; p-value	1.13 [0.11, 12.13], 0.9200		0.94 [0.09, 10.09], 0.9584		1.03 [0.19, 5.51], 0.9749	
OR [95%-CI]; p-value	1.13 [0.10, 12.83], 0.9199		0.94 [0.08, 10.61], 0.9584		1.03 [0.18, 5.72], 0.9749	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9186		-0.00 [-0.05, 0.05], 0.9589		0.00 [-0.04, 0.04], 0.9748	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
RR [95%-CI]; p-value	0.88 [0.03, 25.23], 0.9379		1.15 [0.04, 33.20], 0.9342		1.98 [0.09, 43.11], 0.6638	
OR [95%-CI]; p-value	0.87 [0.03, 26.91], 0.9379		1.16 [0.04, 35.64], 0.9341		2.00 [0.09, 45.18], 0.6568	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.06], 0.9395		0.00 [-0.06, 0.07], 0.9328		0.01 [-0.03, 0.05], 0.6197	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.0492		0.9491		0.2194	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	50/85 (58.8)	29/48 (60.4)	51/98 (52.0)	24/46 (52.2)	101/183 (55.2)	53/94 (56.4)
RR [95%-CI]; p-value	0.97 [0.73, 1.30], 0.8566		1.00 [0.71, 1.40], 0.9881		0.98 [0.79, 1.22], 0.8495	
OR [95%-CI]; p-value	0.94 [0.45, 1.93], 0.8574		0.99 [0.49, 2.01], 0.9881		0.95 [0.58, 1.57], 0.8501	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.16], 0.8571		-0.00 [-0.18, 0.17], 0.9881		-0.01 [-0.14, 0.11], 0.8499	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	32/56 (57.1)	21/24 (87.5)	19/46 (41.3)	11/26 (42.3)	51/102 (50.0)	32/50 (64.0)
RR [95%-CI]; p-value	0.65 [0.50, 0.86], 0.0022		0.98 [0.55, 1.72], 0.9337		0.78 [0.59, 1.04], 0.0889	
OR [95%-CI]; p-value	0.19 [0.05, 0.71], 0.0085		0.96 [0.36, 2.54], 0.9339		0.56 [0.28, 1.13], 0.1034	
RD [95%-CI]; p-value	-0.30 [-0.49, -0.12], 0.0013		-0.01 [-0.25, 0.23], 0.9340		-0.14 [-0.30, 0.02], 0.0957	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.7236		0.1835		0.3042	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	33/85 (38.8)	20/48 (41.7)	34/98 (34.7)	9/46 (19.6)	67/183 (36.6)	29/94 (30.9)
RR [95%-CI]; p-value	0.93 [0.61, 1.43], 0.7463		1.77 [0.93, 3.38], 0.0821		1.19 [0.83, 1.70], 0.3482	
OR [95%-CI]; p-value	0.89 [0.43, 1.83], 0.7477		2.18 [0.94, 5.05], 0.0644		1.29 [0.76, 2.20], 0.3401	
RD [95%-CI]; p-value	-0.03 [-0.20, 0.15], 0.7484		0.15 [0.00, 0.30], 0.0457		0.06 [-0.06, 0.17], 0.3328	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	17/56 (30.4)	9/24 (37.5)	15/46 (32.6)	9/26 (34.6)	32/102 (31.4)	18/50 (36.0)
RR [95%-CI]; p-value	0.81 [0.42, 1.55], 0.5248		0.94 [0.48, 1.84], 0.8617		0.87 [0.55, 1.39], 0.5644	
OR [95%-CI]; p-value	0.73 [0.27, 1.98], 0.5319		0.91 [0.33, 2.53], 0.8623		0.81 [0.40, 1.66], 0.5683	
RD [95%-CI]; p-value	-0.07 [-0.30, 0.16], 0.5393		-0.02 [-0.25, 0.21], 0.8628		-0.05 [-0.21, 0.11], 0.5724	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.3.1.s4
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.8363		0.6160		0.6665	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	4/48 (8.3)	5/98 (5.1)	4/46 (8.7)	15/183 (8.2)	8/94 (8.5)
RR [95%-CI]; p-value	1.41 [0.47, 4.26], 0.5405		0.59 [0.17, 2.08], 0.4096		0.96 [0.42, 2.19], 0.9285	
OR [95%-CI]; p-value	1.47 [0.43, 4.96], 0.5357		0.56 [0.14, 2.21], 0.4062		0.96 [0.39, 2.35], 0.9286	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5176		-0.04 [-0.13, 0.06], 0.4456		-0.00 [-0.07, 0.07], 0.9290	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	2/24 (8.3)	5/46 (10.9)	3/26 (11.5)	13/102 (12.7)	5/50 (10.0)
RR [95%-CI]; p-value	1.71 [0.39, 7.48], 0.4735		0.94 [0.24, 3.63], 0.9308		1.27 [0.48, 3.38], 0.6256	
OR [95%-CI]; p-value	1.83 [0.36, 9.35], 0.4607		0.93 [0.20, 4.27], 0.9309		1.31 [0.44, 3.92], 0.6226	
RD [95%-CI]; p-value	0.06 [-0.08, 0.20], 0.4166		-0.01 [-0.16, 0.15], 0.9314		0.03 [-0.08, 0.13], 0.6096	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_3_1_m_sf_ttl_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7825		0.3848		0.7231	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	5/48 (10.4)	6/98 (6.1)	3/46 (6.5)	12/183 (6.6)	8/94 (8.5)
RR [95%-CI]; p-value	0.68 [0.22, 2.10], 0.5008		0.94 [0.25, 3.59], 0.9264		0.77 [0.33, 1.82], 0.5521	
OR [95%-CI]; p-value	0.65 [0.19, 2.27], 0.4995		0.93 [0.22, 3.92], 0.9265		0.75 [0.30, 1.91], 0.5520	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5194		-0.00 [-0.09, 0.08], 0.9272		-0.02 [-0.09, 0.05], 0.5668	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	4/24 (16.7)	5/46 (10.9)	1/26 (3.8)	10/102 (9.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.54 [0.16, 1.82], 0.3179		2.83 [0.35, 22.91], 0.3305		0.98 [0.35, 2.72], 0.9696	
OR [95%-CI]; p-value	0.49 [0.12, 2.01], 0.3155		3.05 [0.34, 27.62], 0.3003		0.98 [0.32, 3.03], 0.9696	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.09], 0.3631		0.07 [-0.05, 0.19], 0.2371		-0.00 [-0.10, 0.10], 0.9697	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.4542		0.0537		0.1169	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	19/85 (22.4)	13/48 (27.1)	19/98 (19.4)	2/46 (4.3)	38/183 (20.8)	15/94 (16.0)
RR [95%-CI]; p-value	0.83 [0.45, 1.52], 0.5376		4.46 [1.08, 18.34], 0.0383		1.30 [0.76, 2.24], 0.3422	
OR [95%-CI]; p-value	0.78 [0.34, 1.75], 0.5399		5.29 [1.18, 23.78], 0.0171		1.38 [0.72, 2.66], 0.3355	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.11], 0.5466		0.15 [0.05, 0.25], 0.0026		0.05 [-0.05, 0.14], 0.3188	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	9/56 (16.1)	7/24 (29.2)	7/46 (15.2)	5/26 (19.2)	16/102 (15.7)	12/50 (24.0)
RR [95%-CI]; p-value	0.55 [0.23, 1.31], 0.1765		0.79 [0.28, 2.24], 0.6597		0.65 [0.34, 1.27], 0.2119	
OR [95%-CI]; p-value	0.47 [0.15, 1.44], 0.1796		0.75 [0.21, 2.67], 0.6607		0.59 [0.25, 1.36], 0.2141	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.07], 0.2122		-0.04 [-0.22, 0.14], 0.6684		-0.08 [-0.22, 0.05], 0.2371	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.8535		0.8521		0.9699	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	12/85 (14.1)	10/48 (20.8)	11/98 (11.2)	7/46 (15.2)	23/183 (12.6)	17/94 (18.1)
RR [95%-CI]; p-value	0.68 [0.32, 1.45], 0.3162		0.74 [0.31, 1.78], 0.4981		0.69 [0.39, 1.24], 0.2152	
OR [95%-CI]; p-value	0.62 [0.25, 1.58], 0.3168		0.70 [0.25, 1.95], 0.4993		0.65 [0.33, 1.29], 0.2161	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3355		-0.04 [-0.16, 0.08], 0.5183		-0.06 [-0.15, 0.04], 0.2370	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	7/56 (12.5)	5/24 (20.8)	6/46 (13.0)	4/26 (15.4)	13/102 (12.7)	9/50 (18.0)
RR [95%-CI]; p-value	0.60 [0.21, 1.70], 0.3372		0.85 [0.26, 2.73], 0.7822		0.71 [0.32, 1.54], 0.3855	
OR [95%-CI]; p-value	0.54 [0.15, 1.92], 0.3388		0.83 [0.21, 3.24], 0.7826		0.67 [0.26, 1.68], 0.3870	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.10], 0.3750		-0.02 [-0.19, 0.15], 0.7865		-0.05 [-0.18, 0.07], 0.4085	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9492		0.1352		0.3619	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	24/85 (28.2)	14/48 (29.2)	26/98 (26.5)	9/46 (19.6)	50/183 (27.3)	23/94 (24.5)
RR [95%-CI]; p-value	0.97 [0.56, 1.69], 0.9089		1.36 [0.69, 2.66], 0.3746		1.12 [0.73, 1.71], 0.6122	
OR [95%-CI]; p-value	0.96 [0.44, 2.09], 0.9091		1.48 [0.63, 3.49], 0.3636		1.16 [0.66, 2.06], 0.6097	
RD [95%-CI]; p-value	-0.01 [-0.17, 0.15], 0.9093		0.07 [-0.07, 0.21], 0.3436		0.03 [-0.08, 0.14], 0.6053	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	14/56 (25.0)	6/24 (25.0)	7/46 (15.2)	7/26 (26.9)	21/102 (20.6)	13/50 (26.0)
RR [95%-CI]; p-value	1.00 [0.44, 2.29], 1.0000		0.57 [0.22, 1.43], 0.2296		0.79 [0.43, 1.45], 0.4483	
OR [95%-CI]; p-value	1.00 [0.33, 3.02], 1.0000		0.49 [0.15, 1.59], 0.2280		0.74 [0.33, 1.63], 0.4519	
RD [95%-CI]; p-value	0.00 [-0.21, 0.21], 1.0000		-0.12 [-0.32, 0.08], 0.2504		-0.05 [-0.20, 0.09], 0.4636	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.7309		0.9405		0.7863	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	14/85 (16.5)	4/48 (8.3)	8/98 (8.2)	2/46 (4.3)	22/183 (12.0)	6/94 (6.4)
RR [95%-CI]; p-value	1.98 [0.69, 5.67], 0.2049		1.88 [0.42, 8.49], 0.4133		1.88 [0.79, 4.49], 0.1527	
OR [95%-CI]; p-value	2.17 [0.67, 7.01], 0.1877		1.96 [0.40, 9.60], 0.4010		2.00 [0.78, 5.13], 0.1404	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1509		0.04 [-0.04, 0.12], 0.3503		0.06 [-0.01, 0.12], 0.1055	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	3/56 (5.4)	1/24 (4.2)	3/46 (6.5)	1/26 (3.8)	6/102 (5.9)	2/50 (4.0)
RR [95%-CI]; p-value	1.29 [0.14, 11.74], 0.8238		1.70 [0.19, 15.48], 0.6398		1.47 [0.31, 7.03], 0.6289	
OR [95%-CI]; p-value	1.30 [0.13, 13.19], 0.8228		1.74 [0.17, 17.68], 0.6340		1.50 [0.29, 7.71], 0.6253	
RD [95%-CI]; p-value	0.01 [-0.09, 0.11], 0.8143		0.03 [-0.08, 0.13], 0.6098		0.02 [-0.05, 0.09], 0.6031	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.9874		0.2437		0.3967	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	9/85 (10.6)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	16/183 (8.7)	11/94 (11.7)
RR [95%-CI]; p-value	0.85 [0.32, 2.24], 0.7375		0.66 [0.22, 1.96], 0.4515		0.75 [0.36, 1.54], 0.4315	
OR [95%-CI]; p-value	0.83 [0.28, 2.49], 0.7378		0.63 [0.19, 2.11], 0.4506		0.72 [0.32, 1.63], 0.4318	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.10], 0.7427		-0.04 [-0.14, 0.07], 0.4799		-0.03 [-0.11, 0.05], 0.4501	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	2/26 (7.7)	15/102 (14.7)	6/50 (12.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		1.98 [0.44, 8.83], 0.3715		1.23 [0.51, 2.97], 0.6522	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		2.15 [0.41, 11.23], 0.3537		1.26 [0.46, 3.48], 0.6497	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		0.08 [-0.07, 0.22], 0.3118		0.03 [-0.09, 0.14], 0.6397	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.9724		0.9391		0.9504	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	17/85 (20.0)	14/48 (29.2)	18/98 (18.4)	9/46 (19.6)	35/183 (19.1)	23/94 (24.5)
RR [95%-CI]; p-value	0.69 [0.37, 1.27], 0.2273		0.94 [0.46, 1.93], 0.8633		0.78 [0.49, 1.24], 0.2977	
OR [95%-CI]; p-value	0.61 [0.27, 1.38], 0.2298		0.93 [0.38, 2.25], 0.8637		0.73 [0.40, 1.33], 0.3008	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.06], 0.2438		-0.01 [-0.15, 0.13], 0.8648		-0.05 [-0.16, 0.05], 0.3137	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	11/56 (19.6)	7/24 (29.2)	7/46 (15.2)	4/26 (15.4)	18/102 (17.6)	11/50 (22.0)
RR [95%-CI]; p-value	0.67 [0.30, 1.53], 0.3436		0.99 [0.32, 3.06], 0.9849		0.80 [0.41, 1.57], 0.5186	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3499		0.99 [0.26, 3.75], 0.9849		0.76 [0.33, 1.76], 0.5211	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3730		-0.00 [-0.17, 0.17], 0.9849		-0.04 [-0.18, 0.09], 0.5322	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0894		0.8651		0.2899	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	16/85 (18.8)	12/48 (25.0)	13/98 (13.3)	8/46 (17.4)	29/183 (15.8)	20/94 (21.3)
RR [95%-CI]; p-value	0.75 [0.39, 1.46], 0.3991		0.76 [0.34, 1.71], 0.5113		0.74 [0.45, 1.24], 0.2599	
OR [95%-CI]; p-value	0.70 [0.30, 1.63], 0.4014		0.73 [0.28, 1.90], 0.5131		0.70 [0.37, 1.31], 0.2621	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4135		-0.04 [-0.17, 0.09], 0.5291		-0.05 [-0.15, 0.04], 0.2785	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	11/24 (45.8)	9/46 (19.6)	6/26 (23.1)	17/102 (16.7)	17/50 (34.0)
RR [95%-CI]; p-value	0.31 [0.14, 0.68], 0.0032		0.85 [0.34, 2.12], 0.7234		0.49 [0.27, 0.88], 0.0162	
OR [95%-CI]; p-value	0.20 [0.07, 0.59], 0.0024		0.81 [0.25, 2.61], 0.7245		0.39 [0.18, 0.85], 0.0160	
RD [95%-CI]; p-value	-0.32 [-0.53, -0.10], 0.0048		-0.04 [-0.23, 0.16], 0.7287		-0.17 [-0.32, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.0554		0.7179		0.1198	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	4/85 (4.7)	10/48 (20.8)	12/98 (12.2)	5/46 (10.9)	16/183 (8.7)	15/94 (16.0)
RR [95%-CI]; p-value	0.23 [0.07, 0.68], 0.0083		1.13 [0.42, 3.01], 0.8122		0.55 [0.28, 1.06], 0.0736	
OR [95%-CI]; p-value	0.19 [0.06, 0.64], 0.0036		1.14 [0.38, 3.46], 0.8115		0.50 [0.24, 1.07], 0.0713	
RD [95%-CI]; p-value	-0.16 [-0.28, -0.04], 0.0104		0.01 [-0.10, 0.12], 0.8080		-0.07 [-0.16, 0.01], 0.0946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	3/24 (12.5)	8/46 (17.4)	3/26 (11.5)	16/102 (15.7)	6/50 (12.0)
RR [95%-CI]; p-value	1.14 [0.33, 3.94], 0.8325		1.51 [0.44, 5.19], 0.5155		1.31 [0.54, 3.14], 0.5485	
OR [95%-CI]; p-value	1.17 [0.28, 4.84], 0.8317		1.61 [0.39, 6.71], 0.5073		1.36 [0.50, 3.73], 0.5439	
RD [95%-CI]; p-value	0.02 [-0.14, 0.18], 0.8279		0.06 [-0.11, 0.22], 0.4857		0.04 [-0.08, 0.15], 0.5278	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7853		0.5925		0.9762	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	8/48 (16.7)	10/98 (10.2)	3/46 (6.5)	20/183 (10.9)	11/94 (11.7)
RR [95%-CI]; p-value	0.71 [0.30, 1.67], 0.4272		1.56 [0.45, 5.42], 0.4798		0.93 [0.47, 1.87], 0.8466	
OR [95%-CI]; p-value	0.67 [0.24, 1.82], 0.4274		1.63 [0.43, 6.23], 0.4722		0.93 [0.42, 2.02], 0.8468	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.08], 0.4448		0.04 [-0.06, 0.13], 0.4386		-0.01 [-0.09, 0.07], 0.8482	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	4/26 (15.4)	15/102 (14.7)	8/50 (16.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		0.99 [0.32, 3.06], 0.9849		0.92 [0.42, 2.02], 0.8340	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		0.99 [0.26, 3.75], 0.9849		0.91 [0.36, 2.30], 0.8343	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		-0.00 [-0.17, 0.17], 0.9849		-0.01 [-0.14, 0.11], 0.8362	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4512		0.8494		0.5091	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	10/98 (10.2)	4/46 (8.7)	15/183 (8.2)	11/94 (11.7)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.17 [0.39, 3.54], 0.7767		0.70 [0.34, 1.46], 0.3439	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.19 [0.35, 4.03], 0.7757		0.67 [0.30, 1.53], 0.3435	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.02 [-0.09, 0.12], 0.7700		-0.04 [-0.11, 0.04], 0.3671	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	2/24 (8.3)	5/46 (10.9)	2/26 (7.7)	9/102 (8.8)	4/50 (8.0)
RR [95%-CI]; p-value	0.86 [0.17, 4.37], 0.8528		1.41 [0.29, 6.78], 0.6656		1.10 [0.36, 3.41], 0.8648	
OR [95%-CI]; p-value	0.85 [0.14, 4.96], 0.8530		1.46 [0.26, 8.14], 0.6620		1.11 [0.33, 3.81], 0.8646	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8570		0.03 [-0.10, 0.17], 0.6478		0.01 [-0.08, 0.10], 0.8625	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.1.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7430		0.5876		0.8696	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	17/183 (9.3)	11/94 (11.7)
RR [95%-CI]; p-value	0.94 [0.36, 2.43], 0.9003		0.66 [0.22, 1.96], 0.4515		0.79 [0.39, 1.63], 0.5277	
OR [95%-CI]; p-value	0.93 [0.32, 2.75], 0.9004		0.63 [0.19, 2.11], 0.4506		0.77 [0.35, 1.72], 0.5282	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.11], 0.9011		-0.04 [-0.14, 0.07], 0.4799		-0.02 [-0.10, 0.05], 0.5413	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	3/24 (12.5)	4/46 (8.7)	2/26 (7.7)	9/102 (8.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.71 [0.19, 2.75], 0.6250		1.13 [0.22, 5.76], 0.8826		0.88 [0.31, 2.50], 0.8134	
OR [95%-CI]; p-value	0.69 [0.15, 3.13], 0.6256		1.14 [0.19, 6.71], 0.8824		0.87 [0.28, 2.75], 0.8137	
RD [95%-CI]; p-value	-0.04 [-0.19, 0.12], 0.6450		0.01 [-0.12, 0.14], 0.8805		-0.01 [-0.11, 0.09], 0.8171	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_1_m_soc_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.3.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5278		0.5312		0.5768	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	9/48 (18.8)	5/98 (5.1)	0/46 (0.0)	10/183 (5.5)	9/94 (9.6)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		4.74 [0.26, 85.04], 0.2903		0.57 [0.24, 1.36], 0.2041	
OR [95%-CI]; p-value	0.27 [0.09, 0.86], 0.0202		4.95 [0.26, 92.49], 0.2373		0.55 [0.21, 1.39], 0.2001	
RD [95%-CI]; p-value	-0.13 [-0.25, -0.01], 0.0375		0.04 [-0.01, 0.09], 0.1342		-0.04 [-0.11, 0.03], 0.2361	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	3/24 (12.5)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	3/50 (6.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.30], 0.0847		1.15 [0.04, 33.20], 0.9342		0.33 [0.06, 1.89], 0.2121	
OR [95%-CI]; p-value	0.13 [0.01, 1.29], 0.0439		1.16 [0.04, 35.64], 0.9341		0.31 [0.05, 1.94], 0.1896	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1247		0.00 [-0.06, 0.07], 0.9328		-0.04 [-0.11, 0.03], 0.2656	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_3_m_pt_ae10pct_race.sas using SAS 9.4

Table 12.4.4.1.3.s4
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.7405		0.3473		0.2783	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	7/98 (7.1)	2/46 (4.3)	12/183 (6.6)	9/94 (9.6)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.64 [0.36, 7.60], 0.5253		0.68 [0.30, 1.57], 0.3701	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.69 [0.34, 8.48], 0.5182		0.66 [0.27, 1.63], 0.3691	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.03 [-0.05, 0.11], 0.4821		-0.03 [-0.10, 0.04], 0.3946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	3/24 (12.5)	0/46 (0.0)	1/26 (3.8)	2/102 (2.0)	4/50 (8.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.60], 0.1544		0.28 [0.01, 8.05], 0.4573		0.25 [0.05, 1.29], 0.0975	
OR [95%-CI]; p-value	0.26 [0.04, 1.66], 0.1306		0.27 [0.01, 8.39], 0.4267		0.23 [0.04, 1.30], 0.0724	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2144		-0.03 [-0.11, 0.05], 0.4953		-0.06 [-0.14, 0.02], 0.1383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_3_m_pt_ae10pct_race.sas using SAS 9.4

Table 12.4.8.1.1.s4
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.7974		0.7556		0.7759	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	3/48 (6.3)	4/98 (4.1)	2/46 (4.3)	10/183 (5.5)	5/94 (5.3)
RR [95%-CI]; p-value	1.13 [0.30, 4.31], 0.8587		0.94 [0.18, 4.94], 0.9406		1.03 [0.36, 2.92], 0.9597	
OR [95%-CI]; p-value	1.14 [0.27, 4.78], 0.8584		0.94 [0.17, 5.31], 0.9406		1.03 [0.34, 3.10], 0.9596	
RD [95%-CI]; p-value	0.01 [-0.08, 0.10], 0.8562		-0.00 [-0.07, 0.07], 0.9412		0.00 [-0.05, 0.06], 0.9595	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	0/24 (0.0)	1/46 (2.2)	1/26 (3.8)	3/102 (2.9)	1/50 (2.0)
RR [95%-CI]; p-value	1.75 [0.08, 37.41], 0.7202		0.57 [0.04, 8.66], 0.6821		1.47 [0.16, 13.78], 0.7355	
OR [95%-CI]; p-value	1.78 [0.08, 40.91], 0.7157		0.56 [0.03, 9.27], 0.6783		1.48 [0.15, 14.65], 0.7334	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6858		-0.02 [-0.10, 0.07], 0.7001		0.01 [-0.04, 0.06], 0.7165	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_8_1_1_m_soc_sae5pct_race.sas using SAS 9.4

Table 12.4.8.1.2.s4
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_8_1_2_m_pt_sae5pct_race.sas using SAS 9.4

Table 12.4.5.1.1.s4
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_5_1_1_m_soc_aeg35pct_race.sas using SAS 9.4

Table 12.4.5.1.2.s4
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_5_1_2_m_pt_aeg35pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7825		0.3848		0.7231	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	5/48 (10.4)	6/98 (6.1)	3/46 (6.5)	12/183 (6.6)	8/94 (8.5)
RR [95%-CI]; p-value	0.68 [0.22, 2.10], 0.5008		0.94 [0.25, 3.59], 0.9264		0.77 [0.33, 1.82], 0.5521	
OR [95%-CI]; p-value	0.65 [0.19, 2.27], 0.4995		0.93 [0.22, 3.92], 0.9265		0.75 [0.30, 1.91], 0.5520	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5194		-0.00 [-0.09, 0.08], 0.9272		-0.02 [-0.09, 0.05], 0.5668	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	4/24 (16.7)	5/46 (10.9)	1/26 (3.8)	10/102 (9.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.54 [0.16, 1.82], 0.3179		2.83 [0.35, 22.91], 0.3305		0.98 [0.35, 2.72], 0.9696	
OR [95%-CI]; p-value	0.49 [0.12, 2.01], 0.3155		3.05 [0.34, 27.62], 0.3003		0.98 [0.32, 3.03], 0.9696	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.09], 0.3631		0.07 [-0.05, 0.19], 0.2371		-0.00 [-0.10, 0.10], 0.9697	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.4542		0.0537		0.1169	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	19/85 (22.4)	13/48 (27.1)	19/98 (19.4)	2/46 (4.3)	38/183 (20.8)	15/94 (16.0)
RR [95%-CI]; p-value	0.83 [0.45, 1.52], 0.5376		4.46 [1.08, 18.34], 0.0383		1.30 [0.76, 2.24], 0.3422	
OR [95%-CI]; p-value	0.78 [0.34, 1.75], 0.5399		5.29 [1.18, 23.78], 0.0171		1.38 [0.72, 2.66], 0.3355	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.11], 0.5466		0.15 [0.05, 0.25], 0.0026		0.05 [-0.05, 0.14], 0.3188	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	9/56 (16.1)	7/24 (29.2)	7/46 (15.2)	5/26 (19.2)	16/102 (15.7)	12/50 (24.0)
RR [95%-CI]; p-value	0.55 [0.23, 1.31], 0.1765		0.79 [0.28, 2.24], 0.6597		0.65 [0.34, 1.27], 0.2119	
OR [95%-CI]; p-value	0.47 [0.15, 1.44], 0.1796		0.75 [0.21, 2.67], 0.6607		0.59 [0.25, 1.36], 0.2141	
RD [95%-CI]; p-value	-0.13 [-0.34, 0.07], 0.2122		-0.04 [-0.22, 0.14], 0.6684		-0.08 [-0.22, 0.05], 0.2371	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.8535		0.8521		0.9699	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	12/85 (14.1)	10/48 (20.8)	11/98 (11.2)	7/46 (15.2)	23/183 (12.6)	17/94 (18.1)
RR [95%-CI]; p-value	0.68 [0.32, 1.45], 0.3162		0.74 [0.31, 1.78], 0.4981		0.69 [0.39, 1.24], 0.2152	
OR [95%-CI]; p-value	0.62 [0.25, 1.58], 0.3168		0.70 [0.25, 1.95], 0.4993		0.65 [0.33, 1.29], 0.2161	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.07], 0.3355		-0.04 [-0.16, 0.08], 0.5183		-0.06 [-0.15, 0.04], 0.2370	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	7/56 (12.5)	5/24 (20.8)	6/46 (13.0)	4/26 (15.4)	13/102 (12.7)	9/50 (18.0)
RR [95%-CI]; p-value	0.60 [0.21, 1.70], 0.3372		0.85 [0.26, 2.73], 0.7822		0.71 [0.32, 1.54], 0.3855	
OR [95%-CI]; p-value	0.54 [0.15, 1.92], 0.3388		0.83 [0.21, 3.24], 0.7826		0.67 [0.26, 1.68], 0.3870	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.10], 0.3750		-0.02 [-0.19, 0.15], 0.7865		-0.05 [-0.18, 0.07], 0.4085	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9492		0.1352		0.3619	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	24/85 (28.2)	14/48 (29.2)	26/98 (26.5)	9/46 (19.6)	50/183 (27.3)	23/94 (24.5)
RR [95%-CI]; p-value	0.97 [0.56, 1.69], 0.9089		1.36 [0.69, 2.66], 0.3746		1.12 [0.73, 1.71], 0.6122	
OR [95%-CI]; p-value	0.96 [0.44, 2.09], 0.9091		1.48 [0.63, 3.49], 0.3636		1.16 [0.66, 2.06], 0.6097	
RD [95%-CI]; p-value	-0.01 [-0.17, 0.15], 0.9093		0.07 [-0.07, 0.21], 0.3436		0.03 [-0.08, 0.14], 0.6053	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	14/56 (25.0)	6/24 (25.0)	7/46 (15.2)	7/26 (26.9)	21/102 (20.6)	13/50 (26.0)
RR [95%-CI]; p-value	1.00 [0.44, 2.29], 1.0000		0.57 [0.22, 1.43], 0.2296		0.79 [0.43, 1.45], 0.4483	
OR [95%-CI]; p-value	1.00 [0.33, 3.02], 1.0000		0.49 [0.15, 1.59], 0.2280		0.74 [0.33, 1.63], 0.4519	
RD [95%-CI]; p-value	0.00 [-0.21, 0.21], 1.0000		-0.12 [-0.32, 0.08], 0.2504		-0.05 [-0.20, 0.09], 0.4636	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.7309		0.9405		0.7863	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	14/85 (16.5)	4/48 (8.3)	8/98 (8.2)	2/46 (4.3)	22/183 (12.0)	6/94 (6.4)
RR [95%-CI]; p-value	1.98 [0.69, 5.67], 0.2049		1.88 [0.42, 8.49], 0.4133		1.88 [0.79, 4.49], 0.1527	
OR [95%-CI]; p-value	2.17 [0.67, 7.01], 0.1877		1.96 [0.40, 9.60], 0.4010		2.00 [0.78, 5.13], 0.1404	
RD [95%-CI]; p-value	0.08 [-0.03, 0.19], 0.1509		0.04 [-0.04, 0.12], 0.3503		0.06 [-0.01, 0.12], 0.1055	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	3/56 (5.4)	1/24 (4.2)	3/46 (6.5)	1/26 (3.8)	6/102 (5.9)	2/50 (4.0)
RR [95%-CI]; p-value	1.29 [0.14, 11.74], 0.8238		1.70 [0.19, 15.48], 0.6398		1.47 [0.31, 7.03], 0.6289	
OR [95%-CI]; p-value	1.30 [0.13, 13.19], 0.8228		1.74 [0.17, 17.68], 0.6340		1.50 [0.29, 7.71], 0.6253	
RD [95%-CI]; p-value	0.01 [-0.09, 0.11], 0.8143		0.03 [-0.08, 0.13], 0.6098		0.02 [-0.05, 0.09], 0.6031	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.9874		0.2437		0.3967	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	9/85 (10.6)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	16/183 (8.7)	11/94 (11.7)
RR [95%-CI]; p-value	0.85 [0.32, 2.24], 0.7375		0.66 [0.22, 1.96], 0.4515		0.75 [0.36, 1.54], 0.4315	
OR [95%-CI]; p-value	0.83 [0.28, 2.49], 0.7378		0.63 [0.19, 2.11], 0.4506		0.72 [0.32, 1.63], 0.4318	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.10], 0.7427		-0.04 [-0.14, 0.07], 0.4799		-0.03 [-0.11, 0.05], 0.4501	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	2/26 (7.7)	15/102 (14.7)	6/50 (12.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		1.98 [0.44, 8.83], 0.3715		1.23 [0.51, 2.97], 0.6522	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		2.15 [0.41, 11.23], 0.3537		1.26 [0.46, 3.48], 0.6497	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		0.08 [-0.07, 0.22], 0.3118		0.03 [-0.09, 0.14], 0.6397	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.9724		0.9391		0.9504	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	17/85 (20.0)	14/48 (29.2)	18/98 (18.4)	9/46 (19.6)	35/183 (19.1)	23/94 (24.5)
RR [95%-CI]; p-value	0.69 [0.37, 1.27], 0.2273		0.94 [0.46, 1.93], 0.8633		0.78 [0.49, 1.24], 0.2977	
OR [95%-CI]; p-value	0.61 [0.27, 1.38], 0.2298		0.93 [0.38, 2.25], 0.8637		0.73 [0.40, 1.33], 0.3008	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.06], 0.2438		-0.01 [-0.15, 0.13], 0.8648		-0.05 [-0.16, 0.05], 0.3137	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	11/56 (19.6)	7/24 (29.2)	7/46 (15.2)	4/26 (15.4)	18/102 (17.6)	11/50 (22.0)
RR [95%-CI]; p-value	0.67 [0.30, 1.53], 0.3436		0.99 [0.32, 3.06], 0.9849		0.80 [0.41, 1.57], 0.5186	
OR [95%-CI]; p-value	0.59 [0.20, 1.78], 0.3499		0.99 [0.26, 3.75], 0.9849		0.76 [0.33, 1.76], 0.5211	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3730		-0.00 [-0.17, 0.17], 0.9849		-0.04 [-0.18, 0.09], 0.5322	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0894		0.8651		0.2899	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	16/85 (18.8)	12/48 (25.0)	13/98 (13.3)	8/46 (17.4)	29/183 (15.8)	20/94 (21.3)
RR [95%-CI]; p-value	0.75 [0.39, 1.46], 0.3991		0.76 [0.34, 1.71], 0.5113		0.74 [0.45, 1.24], 0.2599	
OR [95%-CI]; p-value	0.70 [0.30, 1.63], 0.4014		0.73 [0.28, 1.90], 0.5131		0.70 [0.37, 1.31], 0.2621	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4135		-0.04 [-0.17, 0.09], 0.5291		-0.05 [-0.15, 0.04], 0.2785	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	11/24 (45.8)	9/46 (19.6)	6/26 (23.1)	17/102 (16.7)	17/50 (34.0)
RR [95%-CI]; p-value	0.31 [0.14, 0.68], 0.0032		0.85 [0.34, 2.12], 0.7234		0.49 [0.27, 0.88], 0.0162	
OR [95%-CI]; p-value	0.20 [0.07, 0.59], 0.0024		0.81 [0.25, 2.61], 0.7245		0.39 [0.18, 0.85], 0.0160	
RD [95%-CI]; p-value	-0.32 [-0.53, -0.10], 0.0048		-0.04 [-0.23, 0.16], 0.7287		-0.17 [-0.32, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.0554		0.7179		0.1198	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	4/85 (4.7)	10/48 (20.8)	12/98 (12.2)	5/46 (10.9)	16/183 (8.7)	15/94 (16.0)
RR [95%-CI]; p-value	0.23 [0.07, 0.68], 0.0083		1.13 [0.42, 3.01], 0.8122		0.55 [0.28, 1.06], 0.0736	
OR [95%-CI]; p-value	0.19 [0.06, 0.64], 0.0036		1.14 [0.38, 3.46], 0.8115		0.50 [0.24, 1.07], 0.0713	
RD [95%-CI]; p-value	-0.16 [-0.28, -0.04], 0.0104		0.01 [-0.10, 0.12], 0.8080		-0.07 [-0.16, 0.01], 0.0946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	3/24 (12.5)	8/46 (17.4)	3/26 (11.5)	16/102 (15.7)	6/50 (12.0)
RR [95%-CI]; p-value	1.14 [0.33, 3.94], 0.8325		1.51 [0.44, 5.19], 0.5155		1.31 [0.54, 3.14], 0.5485	
OR [95%-CI]; p-value	1.17 [0.28, 4.84], 0.8317		1.61 [0.39, 6.71], 0.5073		1.36 [0.50, 3.73], 0.5439	
RD [95%-CI]; p-value	0.02 [-0.14, 0.18], 0.8279		0.06 [-0.11, 0.22], 0.4857		0.04 [-0.08, 0.15], 0.5278	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.2439		0.8808		0.4760	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	7/85 (8.2)	2/48 (4.2)	7/98 (7.1)	4/46 (8.7)	14/183 (7.7)	6/94 (6.4)
RR [95%-CI]; p-value	1.98 [0.43, 9.14], 0.3831		0.82 [0.25, 2.67], 0.7433		1.20 [0.48, 3.02], 0.7007	
OR [95%-CI]; p-value	2.06 [0.41, 10.36], 0.3696		0.81 [0.22, 2.91], 0.7436		1.21 [0.45, 3.27], 0.6996	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.3267		-0.02 [-0.11, 0.08], 0.7514		0.01 [-0.05, 0.08], 0.6918	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	3/24 (12.5)	5/46 (10.9)	3/26 (11.5)	9/102 (8.8)	6/50 (12.0)
RR [95%-CI]; p-value	0.57 [0.14, 2.36], 0.4394		0.94 [0.24, 3.63], 0.9308		0.74 [0.28, 1.95], 0.5369	
OR [95%-CI]; p-value	0.54 [0.11, 2.62], 0.4371		0.93 [0.20, 4.27], 0.9309		0.71 [0.24, 2.12], 0.5373	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.09], 0.4796		-0.01 [-0.16, 0.15], 0.9314		-0.03 [-0.14, 0.07], 0.5553	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.7853		0.5925		0.9762	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	8/48 (16.7)	10/98 (10.2)	3/46 (6.5)	20/183 (10.9)	11/94 (11.7)
RR [95%-CI]; p-value	0.71 [0.30, 1.67], 0.4272		1.56 [0.45, 5.42], 0.4798		0.93 [0.47, 1.87], 0.8466	
OR [95%-CI]; p-value	0.67 [0.24, 1.82], 0.4274		1.63 [0.43, 6.23], 0.4722		0.93 [0.42, 2.02], 0.8468	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.08], 0.4448		0.04 [-0.06, 0.13], 0.4386		-0.01 [-0.09, 0.07], 0.8482	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	8/56 (14.3)	4/24 (16.7)	7/46 (15.2)	4/26 (15.4)	15/102 (14.7)	8/50 (16.0)
RR [95%-CI]; p-value	0.86 [0.29, 2.58], 0.7837		0.99 [0.32, 3.06], 0.9849		0.92 [0.42, 2.02], 0.8340	
OR [95%-CI]; p-value	0.83 [0.23, 3.08], 0.7846		0.99 [0.26, 3.75], 0.9849		0.91 [0.36, 2.30], 0.8343	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7897		-0.00 [-0.17, 0.17], 0.9849		-0.01 [-0.14, 0.11], 0.8362	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4512		0.8494		0.5091	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	10/98 (10.2)	4/46 (8.7)	15/183 (8.2)	11/94 (11.7)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.17 [0.39, 3.54], 0.7767		0.70 [0.34, 1.46], 0.3439	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.19 [0.35, 4.03], 0.7757		0.67 [0.30, 1.53], 0.3435	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.02 [-0.09, 0.12], 0.7700		-0.04 [-0.11, 0.04], 0.3671	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	2/24 (8.3)	5/46 (10.9)	2/26 (7.7)	9/102 (8.8)	4/50 (8.0)
RR [95%-CI]; p-value	0.86 [0.17, 4.37], 0.8528		1.41 [0.29, 6.78], 0.6656		1.10 [0.36, 3.41], 0.8648	
OR [95%-CI]; p-value	0.85 [0.14, 4.96], 0.8530		1.46 [0.26, 8.14], 0.6620		1.11 [0.33, 3.81], 0.8646	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8570		0.03 [-0.10, 0.17], 0.6478		0.01 [-0.08, 0.10], 0.8625	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.2.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7430		0.5876		0.8696	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	6/48 (12.5)	7/98 (7.1)	5/46 (10.9)	17/183 (9.3)	11/94 (11.7)
RR [95%-CI]; p-value	0.94 [0.36, 2.43], 0.9003		0.66 [0.22, 1.96], 0.4515		0.79 [0.39, 1.63], 0.5277	
OR [95%-CI]; p-value	0.93 [0.32, 2.75], 0.9004		0.63 [0.19, 2.11], 0.4506		0.77 [0.35, 1.72], 0.5282	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.11], 0.9011		-0.04 [-0.14, 0.07], 0.4799		-0.02 [-0.10, 0.05], 0.5413	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	3/24 (12.5)	4/46 (8.7)	2/26 (7.7)	9/102 (8.8)	5/50 (10.0)
RR [95%-CI]; p-value	0.71 [0.19, 2.75], 0.6250		1.13 [0.22, 5.76], 0.8826		0.88 [0.31, 2.50], 0.8134	
OR [95%-CI]; p-value	0.69 [0.15, 3.13], 0.6256		1.14 [0.19, 6.71], 0.8824		0.87 [0.28, 2.75], 0.8137	
RD [95%-CI]; p-value	-0.04 [-0.19, 0.12], 0.6450		0.01 [-0.12, 0.14], 0.8805		-0.01 [-0.11, 0.09], 0.8171	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_2_m_soc_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.4.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5278		0.5312		0.5768	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	9/48 (18.8)	5/98 (5.1)	0/46 (0.0)	10/183 (5.5)	9/94 (9.6)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		4.74 [0.26, 85.04], 0.2903		0.57 [0.24, 1.36], 0.2041	
OR [95%-CI]; p-value	0.27 [0.09, 0.86], 0.0202		4.95 [0.26, 92.49], 0.2373		0.55 [0.21, 1.39], 0.2001	
RD [95%-CI]; p-value	-0.13 [-0.25, -0.01], 0.0375		0.04 [-0.01, 0.09], 0.1342		-0.04 [-0.11, 0.03], 0.2361	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	3/24 (12.5)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	3/50 (6.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.30], 0.0847		1.15 [0.04, 33.20], 0.9342		0.33 [0.06, 1.89], 0.2121	
OR [95%-CI]; p-value	0.13 [0.01, 1.29], 0.0439		1.16 [0.04, 35.64], 0.9341		0.31 [0.05, 1.94], 0.1896	
RD [95%-CI]; p-value	-0.11 [-0.24, 0.03], 0.1247		0.00 [-0.06, 0.07], 0.9328		-0.04 [-0.11, 0.03], 0.2656	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_4_m_pt_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.4.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.7405		0.3473		0.2783	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	7/48 (14.6)	7/98 (7.1)	2/46 (4.3)	12/183 (6.6)	9/94 (9.6)
RR [95%-CI]; p-value	0.40 [0.14, 1.20], 0.1031		1.64 [0.36, 7.60], 0.5253		0.68 [0.30, 1.57], 0.3701	
OR [95%-CI]; p-value	0.37 [0.11, 1.22], 0.0926		1.69 [0.34, 8.48], 0.5182		0.66 [0.27, 1.63], 0.3691	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.1267		0.03 [-0.05, 0.11], 0.4821		-0.03 [-0.10, 0.04], 0.3946	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	3/24 (12.5)	0/46 (0.0)	1/26 (3.8)	2/102 (2.0)	4/50 (8.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.60], 0.1544		0.28 [0.01, 8.05], 0.4573		0.25 [0.05, 1.29], 0.0975	
OR [95%-CI]; p-value	0.26 [0.04, 1.66], 0.1306		0.27 [0.01, 8.39], 0.4267		0.23 [0.04, 1.30], 0.0724	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2144		-0.03 [-0.11, 0.05], 0.4953		-0.06 [-0.14, 0.02], 0.1383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_4_m_pt_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.4.s4
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.9034		0.7359		0.7017	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	3/48 (6.3)	5/98 (5.1)	4/46 (8.7)	10/183 (5.5)	7/94 (7.4)
RR [95%-CI]; p-value	0.94 [0.24, 3.77], 0.9317		0.59 [0.17, 2.08], 0.4096		0.73 [0.29, 1.87], 0.5157	
OR [95%-CI]; p-value	0.94 [0.21, 4.11], 0.9318		0.56 [0.14, 2.21], 0.4062		0.72 [0.26, 1.95], 0.5151	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.08], 0.9323		-0.04 [-0.13, 0.06], 0.4456		-0.02 [-0.08, 0.04], 0.5339	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	2/24 (8.3)	3/46 (6.5)	2/26 (7.7)	8/102 (7.8)	4/50 (8.0)
RR [95%-CI]; p-value	1.07 [0.22, 5.14], 0.9313		0.85 [0.15, 4.75], 0.8511		0.98 [0.31, 3.10], 0.9731	
OR [95%-CI]; p-value	1.08 [0.19, 5.99], 0.9312		0.84 [0.13, 5.37], 0.8511		0.98 [0.28, 3.42], 0.9731	
RD [95%-CI]; p-value	0.01 [-0.13, 0.14], 0.9303		-0.01 [-0.14, 0.11], 0.8542		-0.00 [-0.09, 0.09], 0.9732	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_4_m_pt_ae1pct_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.5143		0.1976		0.6952	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	10/85 (11.8)	1/48 (2.1)	4/98 (4.1)	5/46 (10.9)	14/183 (7.7)	6/94 (6.4)
RR [95%-CI]; p-value	5.65 [0.75, 42.78], 0.0938		0.38 [0.11, 1.33], 0.1298		1.20 [0.48, 3.02], 0.7007	
OR [95%-CI]; p-value	6.27 [0.78, 50.55], 0.0516		0.35 [0.09, 1.37], 0.1166		1.21 [0.45, 3.27], 0.6996	
RD [95%-CI]; p-value	0.10 [0.02, 0.18], 0.0170		-0.07 [-0.17, 0.03], 0.1751		0.01 [-0.05, 0.08], 0.6918	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	1/24 (4.2)	5/46 (10.9)	2/26 (7.7)	10/102 (9.8)	3/50 (6.0)
RR [95%-CI]; p-value	2.14 [0.26, 17.38], 0.4754		1.41 [0.29, 6.78], 0.6656		1.63 [0.47, 5.67], 0.4395	
OR [95%-CI]; p-value	2.25 [0.25, 20.41], 0.4587		1.46 [0.26, 8.14], 0.6620		1.70 [0.45, 6.49], 0.4308	
RD [95%-CI]; p-value	0.05 [-0.06, 0.16], 0.3936		0.03 [-0.10, 0.17], 0.6478		0.04 [-0.05, 0.13], 0.3944	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9130		0.5114		0.5226	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	1/183 (0.5)	1/94 (1.1)
RR [95%-CI]; p-value	1.14 [0.04, 33.40], 0.9389		0.23 [0.01, 6.84], 0.3985		0.51 [0.03, 8.12], 0.6362	
OR [95%-CI]; p-value	1.14 [0.04, 34.70], 0.9388		0.23 [0.01, 6.97], 0.3573		0.51 [0.03, 8.26], 0.6301	
RD [95%-CI]; p-value	0.00 [-0.04, 0.04], 0.9377		-0.02 [-0.06, 0.03], 0.4622		-0.01 [-0.03, 0.02], 0.6638	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
RR [95%-CI]; p-value	0.88 [0.03, 25.23], 0.9379		1.15 [0.04, 33.20], 0.9342		1.98 [0.09, 43.11], 0.6638	
OR [95%-CI]; p-value	0.87 [0.03, 26.91], 0.9379		1.16 [0.04, 35.64], 0.9341		2.00 [0.09, 45.18], 0.6568	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.06], 0.9395		0.00 [-0.06, 0.07], 0.9328		0.01 [-0.03, 0.05], 0.6197	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4706		0.4140		0.9794	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	9/85 (10.6)	1/48 (2.1)	4/98 (4.1)	4/46 (8.7)	13/183 (7.1)	5/94 (5.3)
RR [95%-CI]; p-value	5.08 [0.66, 38.91], 0.1175		0.47 [0.12, 1.79], 0.2689		1.34 [0.49, 3.63], 0.5710	
OR [95%-CI]; p-value	5.57 [0.68, 45.35], 0.0740		0.45 [0.11, 1.87], 0.2597		1.36 [0.47, 3.94], 0.5683	
RD [95%-CI]; p-value	0.09 [0.01, 0.16], 0.0301		-0.05 [-0.14, 0.04], 0.3169		0.02 [-0.04, 0.08], 0.5511	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	4/56 (7.1)	1/24 (4.2)	4/46 (8.7)	2/26 (7.7)	8/102 (7.8)	3/50 (6.0)
RR [95%-CI]; p-value	1.71 [0.20, 14.55], 0.6213		1.13 [0.22, 5.76], 0.8826		1.31 [0.36, 4.72], 0.6824	
OR [95%-CI]; p-value	1.77 [0.19, 16.71], 0.6143		1.14 [0.19, 6.71], 0.8824		1.33 [0.34, 5.26], 0.6803	
RD [95%-CI]; p-value	0.03 [-0.07, 0.13], 0.5771		0.01 [-0.12, 0.14], 0.8805		0.02 [-0.07, 0.10], 0.6671	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8012		0.7029		0.8913	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	1/48 (2.1)	1/98 (1.0)	0/46 (0.0)	6/183 (3.3)	1/94 (1.1)
RR [95%-CI]; p-value	2.82 [0.34, 23.47], 0.3367		0.95 [0.03, 27.78], 0.9758		3.08 [0.38, 25.23], 0.2940	
OR [95%-CI]; p-value	2.94 [0.33, 25.91], 0.3107		0.95 [0.03, 28.79], 0.9758		3.15 [0.37, 26.58], 0.2661	
RD [95%-CI]; p-value	0.04 [-0.03, 0.10], 0.2469		-0.00 [-0.04, 0.04], 0.9760		0.02 [-0.01, 0.06], 0.1897	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	0/24 (0.0)	2/46 (4.3)	0/26 (0.0)	4/102 (3.9)	0/50 (0.0)
RR [95%-CI]; p-value	1.75 [0.08, 37.41], 0.7202		2.30 [0.11, 49.24], 0.5931		3.96 [0.21, 73.48], 0.3556	
OR [95%-CI]; p-value	1.78 [0.08, 40.91], 0.7157		2.36 [0.10, 54.43], 0.5802		4.08 [0.21, 78.74], 0.3140	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6858		0.02 [-0.05, 0.10], 0.5387		0.03 [-0.02, 0.08], 0.2169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9495		0.4612		0.6563	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	6/85 (7.1)	5/48 (10.4)	7/98 (7.1)	4/46 (8.7)	13/183 (7.1)	9/94 (9.6)
RR [95%-CI]; p-value	0.68 [0.22, 2.10], 0.5008		0.82 [0.25, 2.67], 0.7433		0.74 [0.33, 1.67], 0.4716	
OR [95%-CI]; p-value	0.65 [0.19, 2.27], 0.4995		0.81 [0.22, 2.91], 0.7436		0.72 [0.30, 1.76], 0.4715	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5194		-0.02 [-0.11, 0.08], 0.7514		-0.02 [-0.09, 0.05], 0.4901	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	6/56 (10.7)	4/24 (16.7)	6/46 (13.0)	2/26 (7.7)	12/102 (11.8)	6/50 (12.0)
RR [95%-CI]; p-value	0.64 [0.20, 2.07], 0.4597		1.70 [0.37, 7.80], 0.4977		0.98 [0.39, 2.46], 0.9663	
OR [95%-CI]; p-value	0.60 [0.15, 2.35], 0.4607		1.80 [0.34, 9.64], 0.4877		0.98 [0.34, 2.78], 0.9664	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4917		0.05 [-0.09, 0.19], 0.4579		-0.00 [-0.11, 0.11], 0.9665	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9130		0.7932		0.6953	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	1/85 (1.2)	0/48 (0.0)	2/98 (2.0)	0/46 (0.0)	3/183 (1.6)	0/94 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.40], 0.9389		1.90 [0.09, 41.27], 0.6834		3.10 [0.16, 61.22], 0.4575	
OR [95%-CI]; p-value	1.14 [0.04, 34.70], 0.9388		1.92 [0.08, 43.36], 0.6775		3.13 [0.16, 63.20], 0.4322	
RD [95%-CI]; p-value	0.00 [-0.04, 0.04], 0.9377		0.01 [-0.03, 0.05], 0.6425		0.01 [-0.01, 0.03], 0.3545	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	1/56 (1.8)	0/24 (0.0)	2/46 (4.3)	1/26 (3.8)	3/102 (2.9)	1/50 (2.0)
RR [95%-CI]; p-value	0.88 [0.03, 25.23], 0.9379		1.13 [0.11, 11.87], 0.9186		1.47 [0.16, 13.78], 0.7355	
OR [95%-CI]; p-value	0.87 [0.03, 26.91], 0.9379		1.14 [0.10, 13.17], 0.9185		1.48 [0.15, 14.65], 0.7334	
RD [95%-CI]; p-value	-0.00 [-0.07, 0.06], 0.9395		0.01 [-0.09, 0.10], 0.9172		0.01 [-0.04, 0.06], 0.7165	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.9517		0.6479		0.8104	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	5/85 (5.9)	5/48 (10.4)	6/98 (6.1)	4/46 (8.7)	11/183 (6.0)	9/94 (9.6)
RR [95%-CI]; p-value	0.56 [0.17, 1.85], 0.3458		0.70 [0.21, 2.37], 0.5716		0.63 [0.27, 1.46], 0.2803	
OR [95%-CI]; p-value	0.54 [0.15, 1.96], 0.3409		0.68 [0.18, 2.56], 0.5711		0.60 [0.24, 1.51], 0.2779	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3734		-0.03 [-0.12, 0.07], 0.5926		-0.04 [-0.10, 0.03], 0.3095	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	5/56 (8.9)	4/24 (16.7)	4/46 (8.7)	2/26 (7.7)	9/102 (8.8)	6/50 (12.0)
RR [95%-CI]; p-value	0.54 [0.16, 1.82], 0.3179		1.13 [0.22, 5.76], 0.8826		0.74 [0.28, 1.95], 0.5369	
OR [95%-CI]; p-value	0.49 [0.12, 2.01], 0.3155		1.14 [0.19, 6.71], 0.8824		0.71 [0.24, 2.12], 0.5373	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.09], 0.3631		0.01 [-0.12, 0.14], 0.8805		-0.03 [-0.14, 0.07], 0.5553	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.7.s4
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.7580		0.6330		0.5308	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	3/85 (3.5)	0/48 (0.0)	3/98 (3.1)	0/46 (0.0)	6/183 (3.3)	0/94 (0.0)
RR [95%-CI]; p-value	3.42 [0.18, 66.93], 0.4172		2.85 [0.15, 55.69], 0.4904		6.20 [0.35, 109.76], 0.2136	
OR [95%-CI]; p-value	3.51 [0.17, 71.61], 0.3849		2.91 [0.14, 59.21], 0.4682		6.37 [0.35, 115.34], 0.1512	
RD [95%-CI]; p-value	0.02 [-0.02, 0.07], 0.3121		0.02 [-0.03, 0.07], 0.3890		0.03 [-0.00, 0.06], 0.0692	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	2/56 (3.6)	0/24 (0.0)	2/46 (4.3)	1/26 (3.8)	4/102 (3.9)	1/50 (2.0)
RR [95%-CI]; p-value	1.75 [0.08, 37.41], 0.7202		1.13 [0.11, 11.87], 0.9186		1.96 [0.22, 17.09], 0.5421	
OR [95%-CI]; p-value	1.78 [0.08, 40.91], 0.7157		1.14 [0.10, 13.17], 0.9185		2.00 [0.22, 18.38], 0.5326	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6858		0.01 [-0.09, 0.10], 0.9172		0.02 [-0.03, 0.07], 0.4862	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_7_m_pt_smq_race.sas using SAS 9.4

Table 12.4.4.1.6.s4
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.8718		0.1497		0.2622	
1.White	N1=85	N1=48	N1=98	N1=46	N1=183	N1=94
n/N1 (%)	15/85 (17.6)	12/48 (25.0)	23/98 (23.5)	5/46 (10.9)	38/183 (20.8)	17/94 (18.1)
RR [95%-CI]; p-value	0.71 [0.36, 1.38], 0.3094		2.16 [0.88, 5.32], 0.0942		1.15 [0.69, 1.92], 0.5990	
OR [95%-CI]; p-value	0.64 [0.27, 1.52], 0.3113		2.51 [0.89, 7.11], 0.0749		1.19 [0.63, 2.24], 0.5965	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.07], 0.3265		0.13 [0.00, 0.25], 0.0447		0.03 [-0.07, 0.12], 0.5901	
2.non-White	N2=56	N2=24	N2=46	N2=26	N2=102	N2=50
n/N2 (%)	9/56 (16.1)	6/24 (25.0)	5/46 (10.9)	4/26 (15.4)	14/102 (13.7)	10/50 (20.0)
RR [95%-CI]; p-value	0.64 [0.26, 1.61], 0.3443		0.71 [0.21, 2.40], 0.5779		0.69 [0.33, 1.43], 0.3171	
OR [95%-CI]; p-value	0.57 [0.18, 1.85], 0.3484		0.67 [0.16, 2.76], 0.5779		0.64 [0.26, 1.55], 0.3189	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.11], 0.3772		-0.05 [-0.21, 0.12], 0.5924		-0.06 [-0.19, 0.07], 0.3420	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_4_1_6_m_pt_adr_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with AE leading to death						
1.White n/N1 (%)	2/85 (2.4)	1/48 (2.1)	2/98 (2.0)	1/46 (2.2)	4/183 (2.2)	2/94 (2.1)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
Number of Patients with AE leading to treatment discontinuation						
1.White n/N1 (%)	11/85 (12.9)	2/48 (4.2)	7/98 (7.1)	3/46 (6.5)	18/183 (9.8)	5/94 (5.3)
2.non-White n/N2 (%)	5/56 (8.9)	3/24 (12.5)	8/46 (17.4)	1/26 (3.8)	13/102 (12.7)	4/50 (8.0)
Number of Patients with AE leading to study discontinuation						
1.White n/N1 (%)	5/85 (5.9)	0/48 (0.0)	3/98 (3.1)	3/46 (6.5)	8/183 (4.4)	3/94 (3.2)
2.non-White n/N2 (%)	3/56 (5.4)	2/24 (8.3)	4/46 (8.7)	0/26 (0.0)	7/102 (6.9)	2/50 (4.0)
Blood and lymphatic system disorders						
Anaemia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	0/183 (0.0)	1/94 (1.1)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Cardiac disorders						
Acute myocardial infarction						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	0/183 (0.0)	1/94 (1.1)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac arrest						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
Cardiac failure congestive						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Gastrointestinal disorders						
Nausea						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	1/98 (1.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Infections and infestations						
Pneumonia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Sepsis						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	1/46 (2.2)	0/183 (0.0)	1/94 (1.1)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Urosepsis						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Wound infection						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Injury, poisoning and procedural complications						
Fall						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	1/98 (1.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Multiple fractures						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Wound						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Blood creatinine increased						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	2/102 (2.0)	0/50 (0.0)
Metabolism and nutrition disorders						
Fluid overload						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Hypercalcaemia						
1.White n/N1 (%)	1/85 (1.2)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Musculoskeletal and connective tissue disorders						
Arthralgia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	1/56 (1.8)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Muscular weakness						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	1/24 (4.2)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	1/50 (2.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.9.1.2.s4
Summary of TEAE Leading to Study Discontinuation by PT
ITT Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Amnesia						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)
Cerebrovascular accident						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	1/24 (4.2)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	1/50 (2.0)
Myasthenia gravis crisis						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	1/98 (1.0)	0/46 (0.0)	1/183 (0.5)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	0/50 (0.0)
Psychiatric disorders						
Hallucination						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	1/24 (4.2)	0/46 (0.0)	0/26 (0.0)	0/102 (0.0)	1/50 (2.0)
Respiratory, thoracic and mediastinal disorders						
Epistaxis						
1.White n/N1 (%)	0/85 (0.0)	0/48 (0.0)	0/98 (0.0)	0/46 (0.0)	0/183 (0.0)	0/94 (0.0)
2.non-White n/N2 (%)	0/56 (0.0)	0/24 (0.0)	1/46 (2.2)	0/26 (0.0)	1/102 (1.0)	0/50 (0.0)

Abbreviations: ER: Extended Release; ITT: Intention-To-Treat; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race/T12_4_9_1_2_m_pt_soc_discon_race.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.8365		0.8824		0.7458	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	50/71 (70.4)	28/36 (77.8)	49/80 (61.3)	21/35 (60.0)	99/151 (65.6)	49/71 (69.0)
RR [95%-CI]; p-value	0.91 [0.72, 1.14], 0.3986		1.02 [0.74, 1.41], 0.9001		0.95 [0.78, 1.15], 0.6043	
OR [95%-CI]; p-value	0.68 [0.27, 1.74], 0.4186		1.05 [0.47, 2.37], 0.8994		0.85 [0.47, 1.56], 0.6109	
RD [95%-CI]; p-value	-0.07 [-0.25, 0.10], 0.4030		0.01 [-0.18, 0.21], 0.8996		-0.03 [-0.17, 0.10], 0.6072	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	51/70 (72.9)	28/36 (77.8)	42/64 (65.6)	23/37 (62.2)	93/134 (69.4)	51/73 (69.9)
RR [95%-CI]; p-value	0.94 [0.75, 1.17], 0.5703		1.06 [0.78, 1.44], 0.7298		0.99 [0.82, 1.20], 0.9451	
OR [95%-CI]; p-value	0.77 [0.30, 1.98], 0.5819		1.16 [0.50, 2.69], 0.7263		0.98 [0.53, 1.82], 0.9452	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5731		0.03 [-0.16, 0.23], 0.7276		-0.00 [-0.14, 0.13], 0.9451	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.3489		0.5307		0.5028	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	7/36 (19.4)	9/80 (11.3)	0/35 (0.0)	17/151 (11.3)	7/71 (9.9)
RR [95%-CI]; p-value	0.58 [0.23, 1.47], 0.2511		7.99 [0.48, 134.03], 0.1487		1.14 [0.50, 2.63], 0.7551	
OR [95%-CI]; p-value	0.53 [0.17, 1.59], 0.2497		8.87 [0.50, 157.50], 0.0757		1.16 [0.46, 2.94], 0.7542	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2813		0.10 [0.02, 0.18], 0.0151		0.01 [-0.07, 0.10], 0.7491	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	4/36 (11.1)	10/64 (15.6)	2/37 (5.4)	19/134 (14.2)	6/73 (8.2)
RR [95%-CI]; p-value	1.16 [0.38, 3.50], 0.7961		2.89 [0.67, 12.49], 0.1551		1.73 [0.72, 4.13], 0.2206	
OR [95%-CI]; p-value	1.18 [0.34, 4.13], 0.7952		3.24 [0.67, 15.68], 0.1262		1.84 [0.70, 4.85], 0.2086	
RD [95%-CI]; p-value	0.02 [-0.11, 0.15], 0.7911		0.10 [-0.01, 0.22], 0.0815		0.06 [-0.03, 0.15], 0.1762	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.7917		0.3100		0.3596	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	4/80 (5.0)	4/35 (11.4)	12/151 (7.9)	7/71 (9.9)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		0.44 [0.12, 1.65], 0.2224		0.81 [0.33, 1.96], 0.6343	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		0.41 [0.10, 1.73], 0.2125		0.79 [0.30, 2.10], 0.6348	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		-0.06 [-0.18, 0.05], 0.2762		-0.02 [-0.10, 0.06], 0.6463	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	3/36 (8.3)	6/64 (9.4)	3/37 (8.1)	16/134 (11.9)	6/73 (8.2)
RR [95%-CI]; p-value	1.71 [0.50, 5.84], 0.3889		1.16 [0.31, 4.35], 0.8300		1.45 [0.59, 3.55], 0.4129	
OR [95%-CI]; p-value	1.83 [0.47, 7.13], 0.3763		1.17 [0.28, 4.99], 0.8295		1.51 [0.57, 4.05], 0.4065	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.3387		0.01 [-0.10, 0.13], 0.8265		0.04 [-0.05, 0.12], 0.3828	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.4398		0.8999		0.6087	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	14/71 (19.7)	7/36 (19.4)	12/80 (15.0)	5/35 (14.3)	26/151 (17.2)	12/71 (16.9)
RR [95%-CI]; p-value	1.01 [0.45, 2.29], 0.9731		1.05 [0.40, 2.76], 0.9210		1.02 [0.55, 1.90], 0.9534	
OR [95%-CI]; p-value	1.02 [0.37, 2.80], 0.9731		1.06 [0.34, 3.27], 0.9209		1.02 [0.48, 2.17], 0.9533	
RD [95%-CI]; p-value	0.00 [-0.16, 0.16], 0.9731		0.01 [-0.13, 0.15], 0.9203		0.00 [-0.10, 0.11], 0.9532	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	16/70 (22.9)	5/36 (13.9)	10/64 (15.6)	6/37 (16.2)	26/134 (19.4)	11/73 (15.1)
RR [95%-CI]; p-value	1.65 [0.66, 4.13], 0.2887		0.96 [0.38, 2.44], 0.9375		1.29 [0.68, 2.45], 0.4422	
OR [95%-CI]; p-value	1.84 [0.61, 5.50], 0.2726		0.96 [0.32, 2.89], 0.9375		1.36 [0.63, 2.93], 0.4367	
RD [95%-CI]; p-value	0.09 [-0.06, 0.24], 0.2406		-0.01 [-0.15, 0.14], 0.9378		0.04 [-0.06, 0.15], 0.4225	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.8889		0.3126		0.5530	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	7/71 (9.9)	2/36 (5.6)	8/80 (10.0)	3/35 (8.6)	15/151 (9.9)	5/71 (7.0)
RR [95%-CI]; p-value	1.77 [0.39, 8.11], 0.4594		1.17 [0.33, 4.14], 0.8114		1.41 [0.53, 3.73], 0.4879	
OR [95%-CI]; p-value	1.86 [0.37, 9.45], 0.4486		1.19 [0.29, 4.76], 0.8106		1.46 [0.51, 4.18], 0.4828	
RD [95%-CI]; p-value	0.04 [-0.06, 0.15], 0.4083		0.01 [-0.10, 0.13], 0.8054		0.03 [-0.05, 0.11], 0.4575	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	3/36 (8.3)	7/64 (10.9)	1/37 (2.7)	16/134 (11.9)	4/73 (5.5)
RR [95%-CI]; p-value	1.54 [0.45, 5.35], 0.4942		4.05 [0.52, 31.62], 0.1826		2.18 [0.76, 6.28], 0.1490	
OR [95%-CI]; p-value	1.62 [0.41, 6.41], 0.4863		4.42 [0.52, 37.44], 0.1398		2.34 [0.75, 7.28], 0.1328	
RD [95%-CI]; p-value	0.05 [-0.07, 0.16], 0.4584		0.08 [-0.01, 0.17], 0.0814		0.06 [-0.01, 0.14], 0.0946	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8700		0.1589		0.2331	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	0/36 (0.0)	3/80 (3.8)	3/35 (8.6)	5/151 (3.3)	3/71 (4.2)
RR [95%-CI]; p-value	2.06 [0.10, 44.44], 0.6457		0.44 [0.09, 2.06], 0.2959		0.78 [0.19, 3.19], 0.7335	
OR [95%-CI]; p-value	2.09 [0.09, 47.50], 0.6374		0.42 [0.08, 2.17], 0.2847		0.78 [0.18, 3.34], 0.7332	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5986		-0.05 [-0.15, 0.05], 0.3526		-0.01 [-0.06, 0.05], 0.7438	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	2/36 (5.6)	4/64 (6.3)	0/37 (0.0)	10/134 (7.5)	2/73 (2.7)
RR [95%-CI]; p-value	1.54 [0.33, 7.26], 0.5832		4.69 [0.25, 86.24], 0.2985		2.72 [0.61, 12.10], 0.1878	
OR [95%-CI]; p-value	1.59 [0.31, 8.33], 0.5777		4.93 [0.25, 96.00], 0.2454		2.86 [0.61, 13.43], 0.1647	
RD [95%-CI]; p-value	0.03 [-0.07, 0.13], 0.5524		0.05 [-0.02, 0.12], 0.1671		0.05 [-0.01, 0.11], 0.1114	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.5010		0.8894		0.3836	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	1/71 (1.4)	1/36 (2.8)	2/80 (2.5)	1/35 (2.9)	3/151 (2.0)	2/71 (2.8)
RR [95%-CI]; p-value	0.51 [0.03, 7.87], 0.6274		0.88 [0.08, 9.34], 0.9120		0.71 [0.12, 4.13], 0.6985	
OR [95%-CI]; p-value	0.50 [0.03, 8.23], 0.6212		0.87 [0.08, 9.94], 0.9120		0.70 [0.11, 4.28], 0.6974	
RD [95%-CI]; p-value	-0.01 [-0.07, 0.05], 0.6561		-0.00 [-0.07, 0.06], 0.9142		-0.01 [-0.05, 0.04], 0.7144	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	1/64 (1.6)	0/37 (0.0)	3/134 (2.2)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		1.17 [0.04, 34.10], 0.9265		3.29 [0.17, 64.82], 0.4334	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		1.17 [0.04, 35.87], 0.9264		3.34 [0.17, 67.67], 0.4044	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.00 [-0.05, 0.05], 0.9249		0.02 [-0.02, 0.05], 0.3293	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.5551		0.4596		0.3124	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	42/71 (59.2)	27/36 (75.0)	39/80 (48.8)	19/35 (54.3)	81/151 (53.6)	46/71 (64.8)
RR [95%-CI]; p-value	0.79 [0.60, 1.03], 0.0850		0.90 [0.62, 1.31], 0.5771		0.83 [0.66, 1.04], 0.1026	
OR [95%-CI]; p-value	0.48 [0.20, 1.18], 0.1056		0.80 [0.36, 1.78], 0.5848		0.63 [0.35, 1.13], 0.1175	
RD [95%-CI]; p-value	-0.16 [-0.34, 0.02], 0.0877		-0.06 [-0.25, 0.14], 0.5839		-0.11 [-0.25, 0.03], 0.1098	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	40/70 (57.1)	23/36 (63.9)	31/64 (48.4)	16/37 (43.2)	71/134 (53.0)	39/73 (53.4)
RR [95%-CI]; p-value	0.89 [0.65, 1.23], 0.4923		1.12 [0.72, 1.75], 0.6192		0.99 [0.76, 1.30], 0.9516	
OR [95%-CI]; p-value	0.75 [0.33, 1.73], 0.5029		1.23 [0.55, 2.78], 0.6141		0.98 [0.55, 1.74], 0.9517	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.13], 0.4979		0.05 [-0.15, 0.25], 0.6128		-0.00 [-0.15, 0.14], 0.9517	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.7129		0.0466		0.1167	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	26/71 (36.6)	14/36 (38.9)	29/80 (36.3)	5/35 (14.3)	55/151 (36.4)	19/71 (26.8)
RR [95%-CI]; p-value	0.94 [0.56, 1.57], 0.8177		2.54 [1.07, 6.01], 0.0342		1.36 [0.88, 2.11], 0.1684	
OR [95%-CI]; p-value	0.91 [0.40, 2.07], 0.8187		3.41 [1.19, 9.76], 0.0175		1.57 [0.84, 2.92], 0.1543	
RD [95%-CI]; p-value	-0.02 [-0.22, 0.17], 0.8193		0.22 [0.06, 0.38], 0.0060		0.10 [-0.03, 0.23], 0.1403	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	24/70 (34.3)	15/36 (41.7)	20/64 (31.3)	13/37 (35.1)	44/134 (32.8)	28/73 (38.4)
RR [95%-CI]; p-value	0.82 [0.50, 1.36], 0.4488		0.89 [0.50, 1.57], 0.6865		0.86 [0.59, 1.25], 0.4209	
OR [95%-CI]; p-value	0.73 [0.32, 1.67], 0.4555		0.84 [0.36, 1.98], 0.6884		0.79 [0.43, 1.42], 0.4256	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.12], 0.4598		-0.04 [-0.23, 0.15], 0.6904		-0.06 [-0.19, 0.08], 0.4296	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.3.1.s5
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.7917		0.3100		0.3596	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	4/80 (5.0)	4/35 (11.4)	12/151 (7.9)	7/71 (9.9)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		0.44 [0.12, 1.65], 0.2224		0.81 [0.33, 1.96], 0.6343	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		0.41 [0.10, 1.73], 0.2125		0.79 [0.30, 2.10], 0.6348	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		-0.06 [-0.18, 0.05], 0.2762		-0.02 [-0.10, 0.06], 0.6463	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	3/36 (8.3)	6/64 (9.4)	3/37 (8.1)	16/134 (11.9)	6/73 (8.2)
RR [95%-CI]; p-value	1.71 [0.50, 5.84], 0.3889		1.16 [0.31, 4.35], 0.8300		1.45 [0.59, 3.55], 0.4129	
OR [95%-CI]; p-value	1.83 [0.47, 7.13], 0.3763		1.17 [0.28, 4.99], 0.8295		1.51 [0.57, 4.05], 0.4065	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.3387		0.01 [-0.10, 0.13], 0.8265		0.04 [-0.05, 0.12], 0.3828	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_3_1_m_sf_ttl_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6240		0.1690		0.1759	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	5/71 (7.0)	5/36 (13.9)	6/80 (7.5)	4/35 (11.4)	11/151 (7.3)	9/71 (12.7)
RR [95%-CI]; p-value	0.51 [0.16, 1.64], 0.2564		0.66 [0.20, 2.18], 0.4919		0.57 [0.25, 1.32], 0.1933	
OR [95%-CI]; p-value	0.47 [0.13, 1.74], 0.2503		0.63 [0.17, 2.38], 0.4915		0.54 [0.21, 1.37], 0.1907	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.06], 0.2933		-0.04 [-0.16, 0.08], 0.5217		-0.05 [-0.14, 0.03], 0.2287	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	4/36 (11.1)	5/64 (7.8)	0/37 (0.0)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	0.77 [0.23, 2.56], 0.6716		5.86 [0.33, 104.28], 0.2287		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	0.75 [0.20, 2.85], 0.6718		6.27 [0.33, 118.15], 0.1640		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.10], 0.6828		0.06 [-0.01, 0.14], 0.0917		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.5931		0.1047		0.1613	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	16/71 (22.5)	10/36 (27.8)	18/80 (22.5)	2/35 (5.7)	34/151 (22.5)	12/71 (16.9)
RR [95%-CI]; p-value	0.81 [0.41, 1.60], 0.5470		3.94 [0.97, 16.06], 0.0560		1.33 [0.74, 2.41], 0.3444	
OR [95%-CI]; p-value	0.76 [0.30, 1.89], 0.5502		4.79 [1.05, 21.92], 0.0289		1.43 [0.69, 2.96], 0.3357	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.12], 0.5586		0.17 [0.05, 0.29], 0.0059		0.06 [-0.05, 0.17], 0.3158	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	10/36 (27.8)	8/64 (12.5)	5/37 (13.5)	20/134 (14.9)	15/73 (20.5)
RR [95%-CI]; p-value	0.62 [0.30, 1.29], 0.1991		0.93 [0.33, 2.62], 0.8834		0.73 [0.40, 1.33], 0.3009	
OR [95%-CI]; p-value	0.54 [0.21, 1.40], 0.2010		0.91 [0.28, 3.03], 0.8835		0.68 [0.32, 1.42], 0.3025	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.2226		-0.01 [-0.15, 0.13], 0.8845		-0.06 [-0.17, 0.05], 0.3190	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9463		0.7196		0.8727	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	10/71 (14.1)	8/36 (22.2)	10/80 (12.5)	5/35 (14.3)	20/151 (13.2)	13/71 (18.3)
RR [95%-CI]; p-value	0.63 [0.27, 1.47], 0.2866		0.88 [0.32, 2.37], 0.7930		0.72 [0.38, 1.37], 0.3204	
OR [95%-CI]; p-value	0.57 [0.20, 1.61], 0.2877		0.86 [0.27, 2.72], 0.7936		0.68 [0.32, 1.46], 0.3225	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3130		-0.02 [-0.15, 0.12], 0.7980		-0.05 [-0.16, 0.05], 0.3442	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	7/36 (19.4)	7/64 (10.9)	6/37 (16.2)	16/134 (11.9)	13/73 (17.8)
RR [95%-CI]; p-value	0.66 [0.27, 1.63], 0.3689		0.67 [0.25, 1.86], 0.4459		0.67 [0.34, 1.32], 0.2451	
OR [95%-CI]; p-value	0.61 [0.21, 1.80], 0.3696		0.63 [0.20, 2.05], 0.4453		0.63 [0.28, 1.39], 0.2452	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.09], 0.3932		-0.05 [-0.19, 0.09], 0.4639		-0.06 [-0.16, 0.04], 0.2666	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9759		0.1504		0.3498	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	19/71 (26.8)	10/36 (27.8)	23/80 (28.8)	7/35 (20.0)	42/151 (27.8)	17/71 (23.9)
RR [95%-CI]; p-value	0.96 [0.50, 1.85], 0.9107		1.44 [0.68, 3.03], 0.3410		1.16 [0.71, 1.89], 0.5470	
OR [95%-CI]; p-value	0.95 [0.39, 2.33], 0.9109		1.61 [0.62, 4.21], 0.3255		1.22 [0.64, 2.35], 0.5426	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9113		0.09 [-0.08, 0.25], 0.3002		0.04 [-0.08, 0.16], 0.5351	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	19/70 (27.1)	10/36 (27.8)	10/64 (15.6)	9/37 (24.3)	29/134 (21.6)	19/73 (26.0)
RR [95%-CI]; p-value	0.98 [0.51, 1.87], 0.9446		0.64 [0.29, 1.44], 0.2809		0.83 [0.50, 1.38], 0.4724	
OR [95%-CI]; p-value	0.97 [0.39, 2.38], 0.9446		0.58 [0.21, 1.58], 0.2811		0.78 [0.40, 1.53], 0.4750	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9448		-0.09 [-0.25, 0.08], 0.2997		-0.04 [-0.17, 0.08], 0.4827	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.5883		0.4690		0.9958	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	7/80 (8.8)	1/35 (2.9)	15/151 (9.9)	4/71 (5.6)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		3.06 [0.39, 23.96], 0.2863		1.76 [0.61, 5.12], 0.2972	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		3.26 [0.39, 27.56], 0.2531		1.85 [0.59, 5.78], 0.2854	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		0.06 [-0.02, 0.14], 0.1638		0.04 [-0.03, 0.11], 0.2404	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	2/36 (5.6)	4/64 (6.3)	2/37 (5.4)	13/134 (9.7)	4/73 (5.5)
RR [95%-CI]; p-value	2.31 [0.53, 10.15], 0.2660		1.16 [0.22, 6.01], 0.8629		1.77 [0.60, 5.23], 0.3015	
OR [95%-CI]; p-value	2.51 [0.51, 12.28], 0.2431		1.17 [0.20, 6.70], 0.8626		1.85 [0.58, 5.91], 0.2905	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.1867		0.01 [-0.09, 0.10], 0.8601		0.04 [-0.03, 0.11], 0.2528	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.8590		0.3315		0.6335	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	5/36 (13.9)	8/80 (10.0)	2/35 (5.7)	16/151 (10.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.81 [0.29, 2.30], 0.6943		1.75 [0.39, 7.83], 0.4640		1.07 [0.46, 2.50], 0.8668	
OR [95%-CI]; p-value	0.79 [0.24, 2.61], 0.6949		1.83 [0.37, 9.11], 0.4529		1.08 [0.42, 2.76], 0.8666	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7031		0.04 [-0.06, 0.14], 0.4064		0.01 [-0.08, 0.09], 0.8650	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	5/36 (13.9)	6/64 (9.4)	5/37 (13.5)	15/134 (11.2)	10/73 (13.7)
RR [95%-CI]; p-value	0.93 [0.33, 2.56], 0.8817		0.69 [0.23, 2.12], 0.5206		0.82 [0.39, 1.73], 0.5966	
OR [95%-CI]; p-value	0.91 [0.28, 2.96], 0.8819		0.66 [0.19, 2.34], 0.5201		0.79 [0.34, 1.87], 0.5972	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.13], 0.8831		-0.04 [-0.17, 0.09], 0.5367		-0.03 [-0.12, 0.07], 0.6063	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.4296		0.0708		0.0651	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	12/71 (16.9)	11/36 (30.6)	10/80 (12.5)	8/35 (22.9)	22/151 (14.6)	19/71 (26.8)
RR [95%-CI]; p-value	0.55 [0.27, 1.13], 0.1036		0.55 [0.24, 1.27], 0.1593		0.54 [0.32, 0.94], 0.0288	
OR [95%-CI]; p-value	0.46 [0.18, 1.19], 0.1043		0.48 [0.17, 1.35], 0.1596		0.47 [0.23, 0.93], 0.0290	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1238		-0.10 [-0.26, 0.05], 0.1956		-0.12 [-0.24, -0.00], 0.0417	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	16/70 (22.9)	10/36 (27.8)	15/64 (23.4)	5/37 (13.5)	31/134 (23.1)	15/73 (20.5)
RR [95%-CI]; p-value	0.82 [0.42, 1.62], 0.5742		1.73 [0.69, 4.39], 0.2447		1.13 [0.65, 1.94], 0.6707	
OR [95%-CI]; p-value	0.77 [0.31, 1.93], 0.5771		1.96 [0.65, 5.92], 0.2279		1.16 [0.58, 2.33], 0.6689	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.5844		0.10 [-0.05, 0.25], 0.1987		0.03 [-0.09, 0.14], 0.6648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4237		0.4432		0.3282	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	14/71 (19.7)	11/36 (30.6)	12/80 (15.0)	5/35 (14.3)	26/151 (17.2)	16/71 (22.5)
RR [95%-CI]; p-value	0.65 [0.33, 1.27], 0.2070		1.05 [0.40, 2.76], 0.9210		0.76 [0.44, 1.33], 0.3422	
OR [95%-CI]; p-value	0.56 [0.22, 1.40], 0.2107		1.06 [0.34, 3.27], 0.9209		0.72 [0.36, 1.44], 0.3455	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2292		0.01 [-0.13, 0.15], 0.9203		-0.05 [-0.17, 0.06], 0.3621	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	12/36 (33.3)	10/64 (15.6)	9/37 (24.3)	20/134 (14.9)	21/73 (28.8)
RR [95%-CI]; p-value	0.43 [0.21, 0.90], 0.0242		0.64 [0.29, 1.44], 0.2809		0.52 [0.30, 0.89], 0.0176	
OR [95%-CI]; p-value	0.33 [0.13, 0.87], 0.0220		0.58 [0.21, 1.58], 0.2811		0.43 [0.22, 0.87], 0.0170	
RD [95%-CI]; p-value	-0.19 [-0.36, -0.02], 0.0324		-0.09 [-0.25, 0.08], 0.2997		-0.14 [-0.26, -0.02], 0.0239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.5274		0.1683		0.1823	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	7/71 (9.9)	6/36 (16.7)	12/80 (15.0)	2/35 (5.7)	19/151 (12.6)	8/71 (11.3)
RR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3102		2.63 [0.62, 11.12], 0.1900		1.12 [0.51, 2.43], 0.7805	
OR [95%-CI]; p-value	0.55 [0.17, 1.77], 0.3085		2.91 [0.62, 13.77], 0.1611		1.13 [0.47, 2.73], 0.7798	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3409		0.09 [-0.02, 0.20], 0.0971		0.01 [-0.08, 0.10], 0.7760	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	7/36 (19.4)	8/64 (12.5)	6/37 (16.2)	13/134 (9.7)	13/73 (17.8)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0679		0.77 [0.29, 2.05], 0.6020		0.54 [0.27, 1.11], 0.0954	
OR [95%-CI]; p-value	0.32 [0.09, 1.09], 0.0584		0.74 [0.23, 2.32], 0.6025		0.50 [0.22, 1.14], 0.0926	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.02], 0.0910		-0.04 [-0.18, 0.11], 0.6124		-0.08 [-0.18, 0.02], 0.1159	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4095		0.3057		0.9116	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	7/36 (19.4)	14/80 (17.5)	4/35 (11.4)	22/151 (14.6)	11/71 (15.5)
RR [95%-CI]; p-value	0.58 [0.23, 1.47], 0.2511		1.53 [0.54, 4.32], 0.4210		0.94 [0.48, 1.83], 0.8566	
OR [95%-CI]; p-value	0.53 [0.17, 1.59], 0.2497		1.64 [0.50, 5.41], 0.4096		0.93 [0.42, 2.04], 0.8568	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2813		0.06 [-0.07, 0.20], 0.3757		-0.01 [-0.11, 0.09], 0.8581	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	5/36 (13.9)	3/64 (4.7)	3/37 (8.1)	13/134 (9.7)	8/73 (11.0)
RR [95%-CI]; p-value	1.03 [0.38, 2.78], 0.9558		0.58 [0.12, 2.72], 0.4879		0.89 [0.38, 2.04], 0.7744	
OR [95%-CI]; p-value	1.03 [0.32, 3.29], 0.9557		0.56 [0.11, 2.91], 0.4835		0.87 [0.34, 2.21], 0.7747	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 0.9556		-0.03 [-0.14, 0.07], 0.5113		-0.01 [-0.10, 0.07], 0.7781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.2987		0.3988		0.8859	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	9/80 (11.3)	2/35 (5.7)	11/151 (7.3)	6/71 (8.5)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		1.97 [0.45, 8.65], 0.3696		0.86 [0.33, 2.24], 0.7603	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		2.09 [0.43, 10.22], 0.3530		0.85 [0.30, 2.40], 0.7606	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.06 [-0.05, 0.16], 0.2944		-0.01 [-0.09, 0.07], 0.7662	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	7/70 (10.0)	5/36 (13.9)	6/64 (9.4)	4/37 (10.8)	13/134 (9.7)	9/73 (12.3)
RR [95%-CI]; p-value	0.72 [0.25, 2.11], 0.5492		0.87 [0.26, 2.88], 0.8158		0.79 [0.35, 1.75], 0.5574	
OR [95%-CI]; p-value	0.69 [0.20, 2.35], 0.5495		0.85 [0.22, 3.24], 0.8159		0.76 [0.31, 1.88], 0.5579	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5667		-0.01 [-0.14, 0.11], 0.8189		-0.03 [-0.12, 0.06], 0.5696	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.1.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4231		0.9943		0.5100	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	5/36 (13.9)	7/80 (8.8)	4/35 (11.4)	13/151 (8.6)	9/71 (12.7)
RR [95%-CI]; p-value	0.61 [0.20, 1.86], 0.3833		0.77 [0.24, 2.45], 0.6525		0.68 [0.30, 1.51], 0.3443	
OR [95%-CI]; p-value	0.57 [0.16, 2.02], 0.3815		0.74 [0.20, 2.72], 0.6532		0.65 [0.26, 1.60], 0.3442	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4129		-0.03 [-0.15, 0.10], 0.6676		-0.04 [-0.13, 0.05], 0.3726	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	4/36 (11.1)	4/64 (6.3)	3/37 (8.1)	13/134 (9.7)	7/73 (9.6)
RR [95%-CI]; p-value	1.16 [0.38, 3.50], 0.7961		0.77 [0.18, 3.26], 0.7234		1.01 [0.42, 2.42], 0.9791	
OR [95%-CI]; p-value	1.18 [0.34, 4.13], 0.7952		0.76 [0.16, 3.58], 0.7232		1.01 [0.39, 2.66], 0.9791	
RD [95%-CI]; p-value	0.02 [-0.11, 0.15], 0.7911		-0.02 [-0.12, 0.09], 0.7314		0.00 [-0.08, 0.09], 0.9791	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_1_m_soc_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.3.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9889		0.5561		0.2832	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	5/80 (6.3)	0/35 (0.0)	7/151 (4.6)	4/71 (5.6)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		4.44 [0.25, 79.06], 0.3106		0.82 [0.25, 2.72], 0.7493	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		4.67 [0.25, 87.80], 0.2596		0.81 [0.23, 2.88], 0.7493	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.05 [-0.02, 0.11], 0.1486		-0.01 [-0.07, 0.05], 0.7571	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	8/36 (22.2)	1/64 (1.6)	0/37 (0.0)	5/134 (3.7)	8/73 (11.0)
RR [95%-CI]; p-value	0.26 [0.08, 0.80], 0.0186		1.17 [0.04, 34.10], 0.9265		0.34 [0.12, 1.00], 0.0506	
OR [95%-CI]; p-value	0.21 [0.06, 0.76], 0.0111		1.17 [0.04, 35.87], 0.9264		0.31 [0.10, 1.00], 0.0406	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0270		0.00 [-0.05, 0.05], 0.9249		-0.07 [-0.15, 0.01], 0.0712	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_3_m_pt_ae10pct_ckd.sas using SAS 9.4

Table 12.4.4.1.3.s5
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4599		0.6195		0.6854	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	6/36 (16.7)	4/80 (5.0)	1/35 (2.9)	7/151 (4.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.25 [0.07, 0.96], 0.0426		1.75 [0.20, 15.10], 0.6108		0.47 [0.17, 1.29], 0.1427	
OR [95%-CI]; p-value	0.22 [0.05, 0.94], 0.0285		1.79 [0.19, 16.61], 0.6041		0.44 [0.15, 1.32], 0.1354	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0615		0.02 [-0.05, 0.09], 0.5650		-0.05 [-0.13, 0.02], 0.1838	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	4/36 (11.1)	3/64 (4.7)	2/37 (5.4)	7/134 (5.2)	6/73 (8.2)
RR [95%-CI]; p-value	0.51 [0.14, 1.94], 0.3258		0.87 [0.15, 4.95], 0.8727		0.64 [0.22, 1.82], 0.3987	
OR [95%-CI]; p-value	0.48 [0.11, 2.06], 0.3192		0.86 [0.14, 5.40], 0.8727		0.62 [0.20, 1.91], 0.3960	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3625		-0.01 [-0.10, 0.08], 0.8749		-0.03 [-0.10, 0.04], 0.4239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_3_m_pt_ae10pct_ckd.sas using SAS 9.4

Table 12.4.8.1.1.s5
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.3830		0.9952		0.5265	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	2/36 (5.6)	2/80 (2.5)	1/35 (2.9)	5/151 (3.3)	3/71 (4.2)
RR [95%-CI]; p-value	0.76 [0.13, 4.35], 0.7584		0.88 [0.08, 9.34], 0.9120		0.78 [0.19, 3.19], 0.7335	
OR [95%-CI]; p-value	0.75 [0.12, 4.70], 0.7581		0.87 [0.08, 9.94], 0.9120		0.78 [0.18, 3.34], 0.7332	
RD [95%-CI]; p-value	-0.01 [-0.10, 0.07], 0.7677		-0.00 [-0.07, 0.06], 0.9142		-0.01 [-0.06, 0.05], 0.7438	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	1/36 (2.8)	3/64 (4.7)	2/37 (5.4)	8/134 (6.0)	3/73 (4.1)
RR [95%-CI]; p-value	2.57 [0.31, 21.19], 0.3801		0.87 [0.15, 4.95], 0.8727		1.45 [0.40, 5.31], 0.5722	
OR [95%-CI]; p-value	2.69 [0.30, 23.96], 0.3570		0.86 [0.14, 5.40], 0.8727		1.48 [0.38, 5.76], 0.5685	
RD [95%-CI]; p-value	0.04 [-0.04, 0.12], 0.2894		-0.01 [-0.10, 0.08], 0.8749		0.02 [-0.04, 0.08], 0.5479	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_8_1_1_m_soc_sae5pct_ckd.sas using SAS 9.4

Table 12.4.8.1.2.s5
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_8_1_2_m_pt_sae5pct_ckd.sas using SAS 9.4

Table 12.4.5.1.1.s5
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_5_1_1_m_soc_aeg35pct_ckd.sas using SAS 9.4

Table 12.4.5.1.2.s5
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_5_1_2_m_pt_aeg35pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6240		0.1690		0.1759	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	5/71 (7.0)	5/36 (13.9)	6/80 (7.5)	4/35 (11.4)	11/151 (7.3)	9/71 (12.7)
RR [95%-CI]; p-value	0.51 [0.16, 1.64], 0.2564		0.66 [0.20, 2.18], 0.4919		0.57 [0.25, 1.32], 0.1933	
OR [95%-CI]; p-value	0.47 [0.13, 1.74], 0.2503		0.63 [0.17, 2.38], 0.4915		0.54 [0.21, 1.37], 0.1907	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.06], 0.2933		-0.04 [-0.16, 0.08], 0.5217		-0.05 [-0.14, 0.03], 0.2287	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	4/36 (11.1)	5/64 (7.8)	0/37 (0.0)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	0.77 [0.23, 2.56], 0.6716		5.86 [0.33, 104.28], 0.2287		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	0.75 [0.20, 2.85], 0.6718		6.27 [0.33, 118.15], 0.1640		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	-0.03 [-0.15, 0.10], 0.6828		0.06 [-0.01, 0.14], 0.0917		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.5931		0.1047		0.1613	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	16/71 (22.5)	10/36 (27.8)	18/80 (22.5)	2/35 (5.7)	34/151 (22.5)	12/71 (16.9)
RR [95%-CI]; p-value	0.81 [0.41, 1.60], 0.5470		3.94 [0.97, 16.06], 0.0560		1.33 [0.74, 2.41], 0.3444	
OR [95%-CI]; p-value	0.76 [0.30, 1.89], 0.5502		4.79 [1.05, 21.92], 0.0289		1.43 [0.69, 2.96], 0.3357	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.12], 0.5586		0.17 [0.05, 0.29], 0.0059		0.06 [-0.05, 0.17], 0.3158	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	10/36 (27.8)	8/64 (12.5)	5/37 (13.5)	20/134 (14.9)	15/73 (20.5)
RR [95%-CI]; p-value	0.62 [0.30, 1.29], 0.1991		0.93 [0.33, 2.62], 0.8834		0.73 [0.40, 1.33], 0.3009	
OR [95%-CI]; p-value	0.54 [0.21, 1.40], 0.2010		0.91 [0.28, 3.03], 0.8835		0.68 [0.32, 1.42], 0.3025	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.2226		-0.01 [-0.15, 0.13], 0.8845		-0.06 [-0.17, 0.05], 0.3190	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.9463		0.7196		0.8727	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	10/71 (14.1)	8/36 (22.2)	10/80 (12.5)	5/35 (14.3)	20/151 (13.2)	13/71 (18.3)
RR [95%-CI]; p-value	0.63 [0.27, 1.47], 0.2866		0.88 [0.32, 2.37], 0.7930		0.72 [0.38, 1.37], 0.3204	
OR [95%-CI]; p-value	0.57 [0.20, 1.61], 0.2877		0.86 [0.27, 2.72], 0.7936		0.68 [0.32, 1.46], 0.3225	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3130		-0.02 [-0.15, 0.12], 0.7980		-0.05 [-0.16, 0.05], 0.3442	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	7/36 (19.4)	7/64 (10.9)	6/37 (16.2)	16/134 (11.9)	13/73 (17.8)
RR [95%-CI]; p-value	0.66 [0.27, 1.63], 0.3689		0.67 [0.25, 1.86], 0.4459		0.67 [0.34, 1.32], 0.2451	
OR [95%-CI]; p-value	0.61 [0.21, 1.80], 0.3696		0.63 [0.20, 2.05], 0.4453		0.63 [0.28, 1.39], 0.2452	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.09], 0.3932		-0.05 [-0.19, 0.09], 0.4639		-0.06 [-0.16, 0.04], 0.2666	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9759		0.1504		0.3498	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	19/71 (26.8)	10/36 (27.8)	23/80 (28.8)	7/35 (20.0)	42/151 (27.8)	17/71 (23.9)
RR [95%-CI]; p-value	0.96 [0.50, 1.85], 0.9107		1.44 [0.68, 3.03], 0.3410		1.16 [0.71, 1.89], 0.5470	
OR [95%-CI]; p-value	0.95 [0.39, 2.33], 0.9109		1.61 [0.62, 4.21], 0.3255		1.22 [0.64, 2.35], 0.5426	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9113		0.09 [-0.08, 0.25], 0.3002		0.04 [-0.08, 0.16], 0.5351	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	19/70 (27.1)	10/36 (27.8)	10/64 (15.6)	9/37 (24.3)	29/134 (21.6)	19/73 (26.0)
RR [95%-CI]; p-value	0.98 [0.51, 1.87], 0.9446		0.64 [0.29, 1.44], 0.2809		0.83 [0.50, 1.38], 0.4724	
OR [95%-CI]; p-value	0.97 [0.39, 2.38], 0.9446		0.58 [0.21, 1.58], 0.2811		0.78 [0.40, 1.53], 0.4750	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9448		-0.09 [-0.25, 0.08], 0.2997		-0.04 [-0.17, 0.08], 0.4827	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.5883		0.4690		0.9958	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	3/36 (8.3)	7/80 (8.8)	1/35 (2.9)	15/151 (9.9)	4/71 (5.6)
RR [95%-CI]; p-value	1.35 [0.38, 4.79], 0.6402		3.06 [0.39, 23.96], 0.2863		1.76 [0.61, 5.12], 0.2972	
OR [95%-CI]; p-value	1.40 [0.35, 5.62], 0.6368		3.26 [0.39, 27.56], 0.2531		1.85 [0.59, 5.78], 0.2854	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.6214		0.06 [-0.02, 0.14], 0.1638		0.04 [-0.03, 0.11], 0.2404	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	2/36 (5.6)	4/64 (6.3)	2/37 (5.4)	13/134 (9.7)	4/73 (5.5)
RR [95%-CI]; p-value	2.31 [0.53, 10.15], 0.2660		1.16 [0.22, 6.01], 0.8629		1.77 [0.60, 5.23], 0.3015	
OR [95%-CI]; p-value	2.51 [0.51, 12.28], 0.2431		1.17 [0.20, 6.70], 0.8626		1.85 [0.58, 5.91], 0.2905	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.1867		0.01 [-0.09, 0.10], 0.8601		0.04 [-0.03, 0.11], 0.2528	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.8590		0.3315		0.6335	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	5/36 (13.9)	8/80 (10.0)	2/35 (5.7)	16/151 (10.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.81 [0.29, 2.30], 0.6943		1.75 [0.39, 7.83], 0.4640		1.07 [0.46, 2.50], 0.8668	
OR [95%-CI]; p-value	0.79 [0.24, 2.61], 0.6949		1.83 [0.37, 9.11], 0.4529		1.08 [0.42, 2.76], 0.8666	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7031		0.04 [-0.06, 0.14], 0.4064		0.01 [-0.08, 0.09], 0.8650	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	5/36 (13.9)	6/64 (9.4)	5/37 (13.5)	15/134 (11.2)	10/73 (13.7)
RR [95%-CI]; p-value	0.93 [0.33, 2.56], 0.8817		0.69 [0.23, 2.12], 0.5206		0.82 [0.39, 1.73], 0.5966	
OR [95%-CI]; p-value	0.91 [0.28, 2.96], 0.8819		0.66 [0.19, 2.34], 0.5201		0.79 [0.34, 1.87], 0.5972	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.13], 0.8831		-0.04 [-0.17, 0.09], 0.5367		-0.03 [-0.12, 0.07], 0.6063	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.4296		0.0708		0.0651	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	12/71 (16.9)	11/36 (30.6)	10/80 (12.5)	8/35 (22.9)	22/151 (14.6)	19/71 (26.8)
RR [95%-CI]; p-value	0.55 [0.27, 1.13], 0.1036		0.55 [0.24, 1.27], 0.1593		0.54 [0.32, 0.94], 0.0288	
OR [95%-CI]; p-value	0.46 [0.18, 1.19], 0.1043		0.48 [0.17, 1.35], 0.1596		0.47 [0.23, 0.93], 0.0290	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1238		-0.10 [-0.26, 0.05], 0.1956		-0.12 [-0.24, -0.00], 0.0417	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	16/70 (22.9)	10/36 (27.8)	15/64 (23.4)	5/37 (13.5)	31/134 (23.1)	15/73 (20.5)
RR [95%-CI]; p-value	0.82 [0.42, 1.62], 0.5742		1.73 [0.69, 4.39], 0.2447		1.13 [0.65, 1.94], 0.6707	
OR [95%-CI]; p-value	0.77 [0.31, 1.93], 0.5771		1.96 [0.65, 5.92], 0.2279		1.16 [0.58, 2.33], 0.6689	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.13], 0.5844		0.10 [-0.05, 0.25], 0.1987		0.03 [-0.09, 0.14], 0.6648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4237		0.4432		0.3282	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	14/71 (19.7)	11/36 (30.6)	12/80 (15.0)	5/35 (14.3)	26/151 (17.2)	16/71 (22.5)
RR [95%-CI]; p-value	0.65 [0.33, 1.27], 0.2070		1.05 [0.40, 2.76], 0.9210		0.76 [0.44, 1.33], 0.3422	
OR [95%-CI]; p-value	0.56 [0.22, 1.40], 0.2107		1.06 [0.34, 3.27], 0.9209		0.72 [0.36, 1.44], 0.3455	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2292		0.01 [-0.13, 0.15], 0.9203		-0.05 [-0.17, 0.06], 0.3621	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	12/36 (33.3)	10/64 (15.6)	9/37 (24.3)	20/134 (14.9)	21/73 (28.8)
RR [95%-CI]; p-value	0.43 [0.21, 0.90], 0.0242		0.64 [0.29, 1.44], 0.2809		0.52 [0.30, 0.89], 0.0176	
OR [95%-CI]; p-value	0.33 [0.13, 0.87], 0.0220		0.58 [0.21, 1.58], 0.2811		0.43 [0.22, 0.87], 0.0170	
RD [95%-CI]; p-value	-0.19 [-0.36, -0.02], 0.0324		-0.09 [-0.25, 0.08], 0.2997		-0.14 [-0.26, -0.02], 0.0239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.5274		0.1683		0.1823	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	7/71 (9.9)	6/36 (16.7)	12/80 (15.0)	2/35 (5.7)	19/151 (12.6)	8/71 (11.3)
RR [95%-CI]; p-value	0.59 [0.21, 1.63], 0.3102		2.63 [0.62, 11.12], 0.1900		1.12 [0.51, 2.43], 0.7805	
OR [95%-CI]; p-value	0.55 [0.17, 1.77], 0.3085		2.91 [0.62, 13.77], 0.1611		1.13 [0.47, 2.73], 0.7798	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3409		0.09 [-0.02, 0.20], 0.0971		0.01 [-0.08, 0.10], 0.7760	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	7/36 (19.4)	8/64 (12.5)	6/37 (16.2)	13/134 (9.7)	13/73 (17.8)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0679		0.77 [0.29, 2.05], 0.6020		0.54 [0.27, 1.11], 0.0954	
OR [95%-CI]; p-value	0.32 [0.09, 1.09], 0.0584		0.74 [0.23, 2.32], 0.6025		0.50 [0.22, 1.14], 0.0926	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.02], 0.0910		-0.04 [-0.18, 0.11], 0.6124		-0.08 [-0.18, 0.02], 0.1159	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.0681		0.4528		0.2902	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	4/71 (5.6)	5/36 (13.9)	8/80 (10.0)	3/35 (8.6)	12/151 (7.9)	8/71 (11.3)
RR [95%-CI]; p-value	0.41 [0.12, 1.42], 0.1578		1.17 [0.33, 4.14], 0.8114		0.71 [0.30, 1.65], 0.4202	
OR [95%-CI]; p-value	0.37 [0.09, 1.47], 0.1460		1.19 [0.29, 4.76], 0.8106		0.68 [0.26, 1.75], 0.4203	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1957		0.01 [-0.10, 0.13], 0.8054		-0.03 [-0.12, 0.05], 0.4453	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	7/70 (10.0)	0/36 (0.0)	4/64 (6.3)	4/37 (10.8)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	7.30 [0.43, 125.08], 0.1703		0.58 [0.15, 2.18], 0.4178		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	8.00 [0.44, 145.13], 0.0985		0.55 [0.13, 2.34], 0.4135		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	0.09 [0.01, 0.17], 0.0339		-0.05 [-0.16, 0.07], 0.4422		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4095		0.3057		0.9116	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	8/71 (11.3)	7/36 (19.4)	14/80 (17.5)	4/35 (11.4)	22/151 (14.6)	11/71 (15.5)
RR [95%-CI]; p-value	0.58 [0.23, 1.47], 0.2511		1.53 [0.54, 4.32], 0.4210		0.94 [0.48, 1.83], 0.8566	
OR [95%-CI]; p-value	0.53 [0.17, 1.59], 0.2497		1.64 [0.50, 5.41], 0.4096		0.93 [0.42, 2.04], 0.8568	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2813		0.06 [-0.07, 0.20], 0.3757		-0.01 [-0.11, 0.09], 0.8581	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	5/36 (13.9)	3/64 (4.7)	3/37 (8.1)	13/134 (9.7)	8/73 (11.0)
RR [95%-CI]; p-value	1.03 [0.38, 2.78], 0.9558		0.58 [0.12, 2.72], 0.4879		0.89 [0.38, 2.04], 0.7744	
OR [95%-CI]; p-value	1.03 [0.32, 3.29], 0.9557		0.56 [0.11, 2.91], 0.4835		0.87 [0.34, 2.21], 0.7747	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 0.9556		-0.03 [-0.14, 0.07], 0.5113		-0.01 [-0.10, 0.07], 0.7781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.2987		0.3988		0.8859	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	9/80 (11.3)	2/35 (5.7)	11/151 (7.3)	6/71 (8.5)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		1.97 [0.45, 8.65], 0.3696		0.86 [0.33, 2.24], 0.7603	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		2.09 [0.43, 10.22], 0.3530		0.85 [0.30, 2.40], 0.7606	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.06 [-0.05, 0.16], 0.2944		-0.01 [-0.09, 0.07], 0.7662	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	7/70 (10.0)	5/36 (13.9)	6/64 (9.4)	4/37 (10.8)	13/134 (9.7)	9/73 (12.3)
RR [95%-CI]; p-value	0.72 [0.25, 2.11], 0.5492		0.87 [0.26, 2.88], 0.8158		0.79 [0.35, 1.75], 0.5574	
OR [95%-CI]; p-value	0.69 [0.20, 2.35], 0.5495		0.85 [0.22, 3.24], 0.8159		0.76 [0.31, 1.88], 0.5579	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5667		-0.01 [-0.14, 0.11], 0.8189		-0.03 [-0.12, 0.06], 0.5696	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.2.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4231		0.9943		0.5100	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	5/36 (13.9)	7/80 (8.8)	4/35 (11.4)	13/151 (8.6)	9/71 (12.7)
RR [95%-CI]; p-value	0.61 [0.20, 1.86], 0.3833		0.77 [0.24, 2.45], 0.6525		0.68 [0.30, 1.51], 0.3443	
OR [95%-CI]; p-value	0.57 [0.16, 2.02], 0.3815		0.74 [0.20, 2.72], 0.6532		0.65 [0.26, 1.60], 0.3442	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4129		-0.03 [-0.15, 0.10], 0.6676		-0.04 [-0.13, 0.05], 0.3726	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	9/70 (12.9)	4/36 (11.1)	4/64 (6.3)	3/37 (8.1)	13/134 (9.7)	7/73 (9.6)
RR [95%-CI]; p-value	1.16 [0.38, 3.50], 0.7961		0.77 [0.18, 3.26], 0.7234		1.01 [0.42, 2.42], 0.9791	
OR [95%-CI]; p-value	1.18 [0.34, 4.13], 0.7952		0.76 [0.16, 3.58], 0.7232		1.01 [0.39, 2.66], 0.9791	
RD [95%-CI]; p-value	0.02 [-0.11, 0.15], 0.7911		-0.02 [-0.12, 0.09], 0.7314		0.00 [-0.08, 0.09], 0.9791	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_2_m_soc_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.4.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9889		0.5561		0.2832	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	4/36 (11.1)	5/80 (6.3)	0/35 (0.0)	7/151 (4.6)	4/71 (5.6)
RR [95%-CI]; p-value	0.25 [0.05, 1.32], 0.1029		4.44 [0.25, 79.06], 0.3106		0.82 [0.25, 2.72], 0.7493	
OR [95%-CI]; p-value	0.23 [0.04, 1.33], 0.0781		4.67 [0.25, 87.80], 0.2596		0.81 [0.23, 2.88], 0.7493	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1381		0.05 [-0.02, 0.11], 0.1486		-0.01 [-0.07, 0.05], 0.7571	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	8/36 (22.2)	1/64 (1.6)	0/37 (0.0)	5/134 (3.7)	8/73 (11.0)
RR [95%-CI]; p-value	0.26 [0.08, 0.80], 0.0186		1.17 [0.04, 34.10], 0.9265		0.34 [0.12, 1.00], 0.0506	
OR [95%-CI]; p-value	0.21 [0.06, 0.76], 0.0111		1.17 [0.04, 35.87], 0.9264		0.31 [0.10, 1.00], 0.0406	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0270		0.00 [-0.05, 0.05], 0.9249		-0.07 [-0.15, 0.01], 0.0712	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_4_m_pt_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.4.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4599		0.6195		0.6854	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	6/36 (16.7)	4/80 (5.0)	1/35 (2.9)	7/151 (4.6)	7/71 (9.9)
RR [95%-CI]; p-value	0.25 [0.07, 0.96], 0.0426		1.75 [0.20, 15.10], 0.6108		0.47 [0.17, 1.29], 0.1427	
OR [95%-CI]; p-value	0.22 [0.05, 0.94], 0.0285		1.79 [0.19, 16.61], 0.6041		0.44 [0.15, 1.32], 0.1354	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0615		0.02 [-0.05, 0.09], 0.5650		-0.05 [-0.13, 0.02], 0.1838	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	4/36 (11.1)	3/64 (4.7)	2/37 (5.4)	7/134 (5.2)	6/73 (8.2)
RR [95%-CI]; p-value	0.51 [0.14, 1.94], 0.3258		0.87 [0.15, 4.95], 0.8727		0.64 [0.22, 1.82], 0.3987	
OR [95%-CI]; p-value	0.48 [0.11, 2.06], 0.3192		0.86 [0.14, 5.40], 0.8727		0.62 [0.20, 1.91], 0.3960	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3625		-0.01 [-0.10, 0.08], 0.8749		-0.03 [-0.10, 0.04], 0.4239	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_4_m_pt_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.4.s5
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.9895		0.3682		0.4560	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	4/71 (5.6)	2/36 (5.6)	4/80 (5.0)	4/35 (11.4)	8/151 (5.3)	6/71 (8.5)
RR [95%-CI]; p-value	1.01 [0.19, 5.28], 0.9867		0.44 [0.12, 1.65], 0.2224		0.63 [0.23, 1.74], 0.3697	
OR [95%-CI]; p-value	1.01 [0.18, 5.82], 0.9867		0.41 [0.10, 1.73], 0.2125		0.61 [0.20, 1.82], 0.3674	
RD [95%-CI]; p-value	0.00 [-0.09, 0.09], 0.9867		-0.06 [-0.18, 0.05], 0.2762		-0.03 [-0.11, 0.04], 0.4031	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	3/36 (8.3)	4/64 (6.3)	2/37 (5.4)	10/134 (7.5)	5/73 (6.8)
RR [95%-CI]; p-value	1.03 [0.27, 3.87], 0.9668		1.16 [0.22, 6.01], 0.8629		1.09 [0.39, 3.07], 0.8710	
OR [95%-CI]; p-value	1.03 [0.24, 4.39], 0.9668		1.17 [0.20, 6.70], 0.8626		1.10 [0.36, 3.34], 0.8708	
RD [95%-CI]; p-value	0.00 [-0.11, 0.11], 0.9666		0.01 [-0.09, 0.10], 0.8601		0.01 [-0.07, 0.08], 0.8693	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_4_m_pt_ae1pct_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.0961		0.6882		0.2988	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	2/36 (5.6)	4/80 (5.0)	2/35 (5.7)	7/151 (4.6)	4/71 (5.6)
RR [95%-CI]; p-value	0.76 [0.13, 4.35], 0.7584		0.88 [0.17, 4.56], 0.8740		0.82 [0.25, 2.72], 0.7493	
OR [95%-CI]; p-value	0.75 [0.12, 4.70], 0.7581		0.87 [0.15, 4.98], 0.8741		0.81 [0.23, 2.88], 0.7493	
RD [95%-CI]; p-value	-0.01 [-0.10, 0.07], 0.7677		-0.01 [-0.10, 0.08], 0.8771		-0.01 [-0.07, 0.05], 0.7571	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	0/36 (0.0)	5/64 (7.8)	5/37 (13.5)	17/134 (12.7)	5/73 (6.8)
RR [95%-CI]; p-value	12.51 [0.76, 205.90], 0.0770		0.58 [0.18, 1.87], 0.3593		1.85 [0.71, 4.82], 0.2061	
OR [95%-CI]; p-value	14.90 [0.85, 259.95], 0.0164		0.54 [0.15, 2.01], 0.3554		1.98 [0.70, 5.60], 0.1929	
RD [95%-CI]; p-value	0.16 [0.06, 0.25], 0.0013		-0.06 [-0.19, 0.07], 0.3837		0.06 [-0.02, 0.14], 0.1569	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5785		0.4886		0.2507	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	0/71 (0.0)	0/36 (0.0)	0/80 (0.0)	1/35 (2.9)	0/151 (0.0)	1/71 (1.4)
RR [95%-CI]; p-value	NA		0.22 [0.01, 6.33], 0.3750		0.23 [0.01, 6.90], 0.4005	
OR [95%-CI]; p-value	NA		0.21 [0.01, 6.49], 0.3293		0.23 [0.01, 6.99], 0.3595	
RD [95%-CI]; p-value	NA		-0.02 [-0.08, 0.04], 0.4483		-0.01 [-0.04, 0.02], 0.4644	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	1/64 (1.6)	0/37 (0.0)	3/134 (2.2)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		1.17 [0.04, 34.10], 0.9265		3.29 [0.17, 64.82], 0.4334	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		1.17 [0.04, 35.87], 0.9264		3.34 [0.17, 67.67], 0.4044	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.00 [-0.05, 0.05], 0.9249		0.02 [-0.02, 0.05], 0.3293	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.1209		0.2952		0.6949	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	2/36 (5.6)	4/80 (5.0)	1/35 (2.9)	7/151 (4.6)	3/71 (4.2)
RR [95%-CI]; p-value	0.76 [0.13, 4.35], 0.7584		1.75 [0.20, 15.10], 0.6108		1.10 [0.29, 4.12], 0.8908	
OR [95%-CI]; p-value	0.75 [0.12, 4.70], 0.7581		1.79 [0.19, 16.61], 0.6041		1.10 [0.28, 4.39], 0.8906	
RD [95%-CI]; p-value	-0.01 [-0.10, 0.07], 0.7677		0.02 [-0.05, 0.09], 0.5650		0.00 [-0.05, 0.06], 0.8889	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	10/70 (14.3)	0/36 (0.0)	4/64 (6.3)	5/37 (13.5)	14/134 (10.4)	5/73 (6.8)
RR [95%-CI]; p-value	10.43 [0.63, 173.55], 0.1022		0.46 [0.13, 1.62], 0.2270		1.53 [0.57, 4.07], 0.3987	
OR [95%-CI]; p-value	12.00 [0.68, 211.68], 0.0338		0.43 [0.11, 1.70], 0.2170		1.59 [0.55, 4.60], 0.3916	
RD [95%-CI]; p-value	0.13 [0.04, 0.22], 0.0050		-0.07 [-0.20, 0.05], 0.2551		0.04 [-0.04, 0.11], 0.3641	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.3892		0.8584		0.4953	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	2/71 (2.8)	1/36 (2.8)	2/80 (2.5)	0/35 (0.0)	4/151 (2.6)	1/71 (1.4)
RR [95%-CI]; p-value	1.01 [0.10, 10.81], 0.9908		1.78 [0.08, 38.38], 0.7144		1.88 [0.21, 16.52], 0.5689	
OR [95%-CI]; p-value	1.01 [0.09, 11.58], 0.9908		1.79 [0.08, 40.83], 0.7099		1.90 [0.21, 17.36], 0.5612	
RD [95%-CI]; p-value	0.00 [-0.07, 0.07], 0.9907		0.01 [-0.04, 0.06], 0.6790		0.01 [-0.03, 0.05], 0.5169	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	5/70 (7.1)	0/36 (0.0)	1/64 (1.6)	0/37 (0.0)	6/134 (4.5)	0/73 (0.0)
RR [95%-CI]; p-value	5.21 [0.29, 92.84], 0.2610		1.17 [0.04, 34.10], 0.9265		6.58 [0.37, 116.20], 0.1983	
OR [95%-CI]; p-value	5.54 [0.29, 104.29], 0.2014		1.17 [0.04, 35.87], 0.9264		6.84 [0.38, 124.29], 0.1331	
RD [95%-CI]; p-value	0.06 [-0.01, 0.13], 0.1118		0.00 [-0.05, 0.05], 0.9249		0.04 [-0.00, 0.08], 0.0611	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.1798		0.6142		0.1767	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	7/36 (19.4)	8/80 (10.0)	4/35 (11.4)	14/151 (9.3)	11/71 (15.5)
RR [95%-CI]; p-value	0.43 [0.16, 1.20], 0.1072		0.88 [0.28, 2.72], 0.8173		0.60 [0.29, 1.25], 0.1725	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1000		0.86 [0.24, 3.07], 0.8176		0.56 [0.24, 1.30], 0.1714	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.03], 0.1361		-0.01 [-0.14, 0.11], 0.8217		-0.06 [-0.16, 0.03], 0.2042	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	6/70 (8.6)	2/36 (5.6)	5/64 (7.8)	2/37 (5.4)	11/134 (8.2)	4/73 (5.5)
RR [95%-CI]; p-value	1.54 [0.33, 7.26], 0.5832		1.45 [0.30, 7.08], 0.6496		1.50 [0.49, 4.54], 0.4747	
OR [95%-CI]; p-value	1.59 [0.31, 8.33], 0.5777		1.48 [0.27, 8.06], 0.6463		1.54 [0.47, 5.03], 0.4692	
RD [95%-CI]; p-value	0.03 [-0.07, 0.13], 0.5524		0.02 [-0.07, 0.12], 0.6307		0.03 [-0.04, 0.10], 0.4440	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5785		0.6186		0.4238	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	0/71 (0.0)	0/36 (0.0)	2/80 (2.5)	1/35 (2.9)	2/151 (1.3)	1/71 (1.4)
RR [95%-CI]; p-value	NA		0.88 [0.08, 9.34], 0.9120		0.94 [0.09, 10.20], 0.9597	
OR [95%-CI]; p-value	NA		0.87 [0.08, 9.94], 0.9120		0.94 [0.08, 10.54], 0.9597	
RD [95%-CI]; p-value	NA		-0.00 [-0.07, 0.06], 0.9142		-0.00 [-0.03, 0.03], 0.9601	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	2/64 (3.1)	0/37 (0.0)	4/134 (3.0)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		2.34 [0.11, 50.62], 0.5869		4.39 [0.24, 81.86], 0.3219	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		2.39 [0.10, 54.36], 0.5741		4.49 [0.23, 86.16], 0.2756	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.02 [-0.04, 0.07], 0.5325		0.02 [-0.01, 0.06], 0.1891	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.3831		0.9072		0.4536	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	6/71 (8.5)	7/36 (19.4)	7/80 (8.8)	4/35 (11.4)	13/151 (8.6)	11/71 (15.5)
RR [95%-CI]; p-value	0.43 [0.16, 1.20], 0.1072		0.77 [0.24, 2.45], 0.6525		0.56 [0.26, 1.18], 0.1256	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1000		0.74 [0.20, 2.72], 0.6532		0.51 [0.22, 1.21], 0.1234	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.03], 0.1361		-0.03 [-0.15, 0.10], 0.6676		-0.07 [-0.16, 0.03], 0.1569	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	4/70 (5.7)	2/36 (5.6)	3/64 (4.7)	2/37 (5.4)	7/134 (5.2)	4/73 (5.5)
RR [95%-CI]; p-value	1.03 [0.20, 5.35], 0.9733		0.87 [0.15, 4.95], 0.8727		0.95 [0.29, 3.15], 0.9376	
OR [95%-CI]; p-value	1.03 [0.18, 5.91], 0.9733		0.86 [0.14, 5.40], 0.8727		0.95 [0.27, 3.36], 0.9376	
RD [95%-CI]; p-value	0.00 [-0.09, 0.09], 0.9732		-0.01 [-0.10, 0.08], 0.8749		-0.00 [-0.07, 0.06], 0.9380	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.7.s5
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8575		0.7646		0.8100	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	3/71 (4.2)	0/36 (0.0)	3/80 (3.8)	1/35 (2.9)	6/151 (4.0)	1/71 (1.4)
RR [95%-CI]; p-value	3.08 [0.16, 59.95], 0.4569		1.31 [0.14, 12.18], 0.8109		2.82 [0.35, 23.00], 0.3326	
OR [95%-CI]; p-value	3.18 [0.15, 65.16], 0.4295		1.32 [0.13, 13.20], 0.8100		2.90 [0.34, 24.52], 0.3077	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.3517		0.01 [-0.06, 0.08], 0.8002		0.03 [-0.02, 0.07], 0.2257	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	2/70 (2.9)	0/36 (0.0)	2/64 (3.1)	0/37 (0.0)	4/134 (3.0)	0/73 (0.0)
RR [95%-CI]; p-value	2.09 [0.10, 45.07], 0.6392		2.34 [0.11, 50.62], 0.5869		4.39 [0.24, 81.86], 0.3219	
OR [95%-CI]; p-value	2.12 [0.09, 48.21], 0.6304		2.39 [0.10, 54.36], 0.5741		4.49 [0.23, 86.16], 0.2756	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.5912		0.02 [-0.04, 0.07], 0.5325		0.02 [-0.01, 0.06], 0.1891	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_7_m_pt_smq_ckd.sas using SAS 9.4

Table 12.4.4.1.6.s5
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.7064		0.3421		0.2831	
1.CKD Stage 3	N1=71	N1=36	N1=80	N1=35	N1=151	N1=71
n/N1 (%)	12/71 (16.9)	8/36 (22.2)	19/80 (23.8)	4/35 (11.4)	31/151 (20.5)	12/71 (16.9)
RR [95%-CI]; p-value	0.76 [0.34, 1.69], 0.5023		2.08 [0.76, 5.66], 0.1526		1.21 [0.66, 2.22], 0.5278	
OR [95%-CI]; p-value	0.71 [0.26, 1.94], 0.5047		2.41 [0.76, 7.71], 0.1285		1.27 [0.61, 2.65], 0.5234	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5181		0.12 [-0.02, 0.26], 0.0862		0.04 [-0.07, 0.14], 0.5118	
2.CKD Stage 4	N2=70	N2=36	N2=64	N2=37	N2=134	N2=73
n/N2 (%)	12/70 (17.1)	10/36 (27.8)	9/64 (14.1)	5/37 (13.5)	21/134 (15.7)	15/73 (20.5)
RR [95%-CI]; p-value	0.62 [0.30, 1.29], 0.1991		1.04 [0.38, 2.87], 0.9387		0.76 [0.42, 1.39], 0.3747	
OR [95%-CI]; p-value	0.54 [0.21, 1.40], 0.2010		1.05 [0.32, 3.40], 0.9387		0.72 [0.34, 1.50], 0.3765	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.2226		0.01 [-0.13, 0.14], 0.9384		-0.05 [-0.16, 0.06], 0.3904	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd/T12_4_4_1_6_m_pt_adr_ckd.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.6730		0.3370		0.8882	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	30/43 (69.8)	20/26 (76.9)	32/53 (60.4)	9/20 (45.0)	62/96 (64.6)	29/46 (63.0)
RR [95%-CI]; p-value	0.91 [0.68, 1.21], 0.5066		1.34 [0.79, 2.28], 0.2782		1.02 [0.78, 1.34], 0.8590	
OR [95%-CI]; p-value	0.69 [0.23, 2.12], 0.5191		1.86 [0.66, 5.26], 0.2376		1.07 [0.51, 2.22], 0.8579	
RD [95%-CI]; p-value	-0.07 [-0.28, 0.14], 0.5089		0.15 [-0.10, 0.41], 0.2367		0.02 [-0.15, 0.18], 0.8584	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	37/50 (74.0)	16/22 (72.7)	27/44 (61.4)	20/28 (71.4)	64/94 (68.1)	36/50 (72.0)
RR [95%-CI]; p-value	1.02 [0.75, 1.38], 0.9110		0.86 [0.62, 1.20], 0.3691		0.95 [0.76, 1.18], 0.6207	
OR [95%-CI]; p-value	1.07 [0.34, 3.31], 0.9101		0.64 [0.23, 1.76], 0.3818		0.83 [0.39, 1.76], 0.6273	
RD [95%-CI]; p-value	0.01 [-0.21, 0.24], 0.9107		-0.10 [-0.32, 0.12], 0.3714		-0.04 [-0.20, 0.12], 0.6231	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	34/48 (70.8)	20/24 (83.3)	32/47 (68.1)	15/24 (62.5)	66/95 (69.5)	35/48 (72.9)
RR [95%-CI]; p-value	0.85 [0.66, 1.10], 0.2114		1.09 [0.76, 1.57], 0.6472		0.95 [0.77, 1.18], 0.6636	
OR [95%-CI]; p-value	0.49 [0.14, 1.68], 0.2482		1.28 [0.46, 3.58], 0.6379		0.85 [0.39, 1.83], 0.6695	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.07], 0.2134		0.06 [-0.18, 0.29], 0.6415		-0.03 [-0.19, 0.12], 0.6656	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.8478		0.4543		0.3169	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	3/26 (11.5)	3/53 (5.7)	1/20 (5.0)	6/96 (6.3)	4/46 (8.7)
RR [95%-CI]; p-value	0.60 [0.13, 2.78], 0.5177		1.13 [0.12, 10.26], 0.9122		0.72 [0.21, 2.42], 0.5943	
OR [95%-CI]; p-value	0.58 [0.11, 3.09], 0.5146		1.14 [0.11, 11.65], 0.9120		0.70 [0.19, 2.61], 0.5940	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.10], 0.5361		0.01 [-0.11, 0.12], 0.9096		-0.02 [-0.12, 0.07], 0.6129	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	7/50 (14.0)	3/22 (13.6)	8/44 (18.2)	0/28 (0.0)	15/94 (16.0)	3/50 (6.0)
RR [95%-CI]; p-value	1.03 [0.29, 3.61], 0.9672		10.36 [0.62, 173.52], 0.1039		2.66 [0.81, 8.75], 0.1075	
OR [95%-CI]; p-value	1.03 [0.24, 4.42], 0.9672		12.44 [0.69, 226.05], 0.0337		2.97 [0.82, 10.82], 0.0854	
RD [95%-CI]; p-value	0.00 [-0.17, 0.18], 0.9671		0.16 [0.04, 0.29], 0.0093		0.10 [0.00, 0.20], 0.0488	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	5/24 (20.8)	8/47 (17.0)	1/24 (4.2)	15/95 (15.8)	6/48 (12.5)
RR [95%-CI]; p-value	0.70 [0.25, 1.98], 0.5006		4.09 [0.54, 30.79], 0.1721		1.26 [0.52, 3.05], 0.6032	
OR [95%-CI]; p-value	0.65 [0.18, 2.31], 0.5023		4.72 [0.55, 40.17], 0.1236		1.31 [0.47, 3.63], 0.5997	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5206		0.13 [-0.01, 0.26], 0.0599		0.03 [-0.09, 0.15], 0.5876	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.4972		0.4441		0.2234	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	3/26 (11.5)	2/53 (3.8)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.81 [0.20, 3.32], 0.7655		0.38 [0.06, 2.50], 0.3125		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.79 [0.16, 3.83], 0.7656		0.35 [0.05, 2.69], 0.2972		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.13], 0.7707		-0.06 [-0.20, 0.08], 0.3872		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	0/22 (0.0)	5/44 (11.4)	2/28 (7.1)	11/94 (11.7)	2/50 (4.0)
RR [95%-CI]; p-value	5.40 [0.31, 92.59], 0.2448		1.59 [0.33, 7.65], 0.5621		2.93 [0.67, 12.69], 0.1515	
OR [95%-CI]; p-value	6.00 [0.32, 112.37], 0.1776		1.67 [0.30, 9.25], 0.5556		3.18 [0.68, 14.96], 0.1247	
RD [95%-CI]; p-value	0.10 [-0.01, 0.21], 0.0780		0.04 [-0.09, 0.18], 0.5363		0.08 [-0.01, 0.16], 0.0747	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	3/24 (12.5)	3/47 (6.4)	3/24 (12.5)	11/95 (11.6)	6/48 (12.5)
RR [95%-CI]; p-value	1.33 [0.39, 4.58], 0.6475		0.51 [0.11, 2.34], 0.3870		0.93 [0.36, 2.35], 0.8722	
OR [95%-CI]; p-value	1.40 [0.34, 5.84], 0.6432		0.48 [0.09, 2.57], 0.3807		0.92 [0.32, 2.65], 0.8723	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6293		-0.06 [-0.21, 0.09], 0.4230		-0.01 [-0.12, 0.10], 0.8737	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.4906		0.3467		0.5802	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	6/43 (14.0)	5/26 (19.2)	6/53 (11.3)	1/20 (5.0)	12/96 (12.5)	6/46 (13.0)
RR [95%-CI]; p-value	0.73 [0.25, 2.14], 0.5613		2.26 [0.29, 17.65], 0.4354		0.96 [0.38, 2.39], 0.9273	
OR [95%-CI]; p-value	0.68 [0.19, 2.50], 0.5617		2.43 [0.27, 21.52], 0.4133		0.95 [0.33, 2.72], 0.9274	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.13], 0.5730		0.06 [-0.06, 0.19], 0.3334		-0.01 [-0.12, 0.11], 0.9279	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	12/50 (24.0)	3/22 (13.6)	9/44 (20.5)	4/28 (14.3)	21/94 (22.3)	7/50 (14.0)
RR [95%-CI]; p-value	1.76 [0.55, 5.62], 0.3401		1.43 [0.49, 4.21], 0.5141		1.60 [0.73, 3.49], 0.2424	
OR [95%-CI]; p-value	2.00 [0.50, 7.95], 0.3185		1.54 [0.43, 5.59], 0.5071		1.77 [0.69, 4.50], 0.2286	
RD [95%-CI]; p-value	0.10 [-0.08, 0.29], 0.2747		0.06 [-0.11, 0.24], 0.4923		0.08 [-0.04, 0.21], 0.2010	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	12/48 (25.0)	4/24 (16.7)	7/47 (14.9)	6/24 (25.0)	19/95 (20.0)	10/48 (20.8)
RR [95%-CI]; p-value	1.50 [0.54, 4.16], 0.4359		0.60 [0.23, 1.58], 0.2969		0.96 [0.49, 1.90], 0.9067	
OR [95%-CI]; p-value	1.67 [0.47, 5.86], 0.4227		0.53 [0.15, 1.79], 0.2976		0.95 [0.40, 2.24], 0.9068	
RD [95%-CI]; p-value	0.08 [-0.11, 0.28], 0.3973		-0.10 [-0.30, 0.10], 0.3242		-0.01 [-0.15, 0.13], 0.9073	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9106		0.2898		0.3848	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	2/26 (7.7)	3/53 (5.7)	2/20 (10.0)	8/96 (8.3)	4/46 (8.7)
RR [95%-CI]; p-value	1.51 [0.32, 7.24], 0.6050		0.57 [0.10, 3.14], 0.5151		0.96 [0.30, 3.02], 0.9421	
OR [95%-CI]; p-value	1.58 [0.28, 8.80], 0.5998		0.54 [0.08, 3.50], 0.5127		0.95 [0.27, 3.35], 0.9421	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5823		-0.04 [-0.19, 0.10], 0.5587		-0.00 [-0.10, 0.09], 0.9425	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	0/22 (0.0)	6/44 (13.6)	1/28 (3.6)	9/94 (9.6)	1/50 (2.0)
RR [95%-CI]; p-value	2.70 [0.14, 51.70], 0.5096		3.82 [0.49, 30.06], 0.2031		4.79 [0.62, 36.72], 0.1319	
OR [95%-CI]; p-value	2.81 [0.13, 58.50], 0.4875		4.26 [0.48, 37.48], 0.1599		5.19 [0.64, 42.19], 0.0887	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4090		0.10 [-0.02, 0.22], 0.1073		0.08 [0.00, 0.15], 0.0366	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	3/24 (12.5)	6/47 (12.8)	1/24 (4.2)	14/95 (14.7)	4/48 (8.3)
RR [95%-CI]; p-value	1.33 [0.39, 4.58], 0.6475		3.06 [0.39, 24.02], 0.2865		1.77 [0.62, 5.08], 0.2898	
OR [95%-CI]; p-value	1.40 [0.34, 5.84], 0.6432		3.37 [0.38, 29.71], 0.2502		1.90 [0.59, 6.13], 0.2757	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6293		0.09 [-0.04, 0.21], 0.1757		0.06 [-0.04, 0.17], 0.2355	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.6813		0.1695		0.6155	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	0/26 (0.0)	0/53 (0.0)	2/20 (10.0)	3/96 (3.1)	2/46 (4.3)
RR [95%-CI]; p-value	3.70 [0.19, 70.97], 0.3857		0.09 [0.00, 1.99], 0.1285		0.72 [0.12, 4.15], 0.7122	
OR [95%-CI]; p-value	3.90 [0.19, 81.07], 0.3460		0.08 [0.00, 1.97], 0.0564		0.71 [0.11, 4.40], 0.7114	
RD [95%-CI]; p-value	0.05 [-0.04, 0.14], 0.2787		-0.09 [-0.22, 0.04], 0.1848		-0.01 [-0.08, 0.06], 0.7262	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	3/44 (6.8)	1/28 (3.6)	3/94 (3.2)	1/50 (2.0)
RR [95%-CI]; p-value	0.45 [0.01, 21.76], 0.6836		1.91 [0.21, 17.46], 0.5669		1.60 [0.17, 14.94], 0.6822	
OR [95%-CI]; p-value	0.44 [0.01, 22.89], 0.6758		1.98 [0.20, 20.00], 0.5577		1.62 [0.16, 15.95], 0.6787	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.7175		0.03 [-0.07, 0.13], 0.5301		0.01 [-0.04, 0.06], 0.6572	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	2/24 (8.3)	4/47 (8.5)	0/24 (0.0)	9/95 (9.5)	2/48 (4.2)
RR [95%-CI]; p-value	1.25 [0.26, 5.98], 0.7799		4.17 [0.23, 75.72], 0.3343		2.27 [0.51, 10.11], 0.2807	
OR [95%-CI]; p-value	1.28 [0.23, 7.13], 0.7785		4.47 [0.23, 88.09], 0.2850		2.41 [0.50, 11.61], 0.2607	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7711		0.06 [-0.03, 0.16], 0.1932		0.05 [-0.03, 0.13], 0.2026	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.9103		0.5562		0.5854	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	1/26 (3.8)	0/53 (0.0)	1/20 (5.0)	2/96 (2.1)	2/46 (4.3)
RR [95%-CI]; p-value	1.21 [0.12, 12.69], 0.8741		0.19 [0.01, 5.36], 0.3273		0.48 [0.07, 3.30], 0.4546	
OR [95%-CI]; p-value	1.22 [0.11, 14.15], 0.8738		0.18 [0.01, 5.56], 0.2726		0.47 [0.06, 3.43], 0.4453	
RD [95%-CI]; p-value	0.01 [-0.09, 0.11], 0.8709		-0.04 [-0.14, 0.06], 0.4206		-0.02 [-0.09, 0.04], 0.4980	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	1/44 (2.3)	0/28 (0.0)	1/94 (1.1)	0/50 (0.0)
RR [95%-CI]; p-value	0.45 [0.01, 21.76], 0.6836		1.30 [0.04, 37.37], 0.8800		1.07 [0.04, 31.48], 0.9668	
OR [95%-CI]; p-value	0.44 [0.01, 22.89], 0.6758		1.30 [0.04, 40.13], 0.8796		1.08 [0.04, 32.61], 0.9667	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.7175		0.01 [-0.06, 0.07], 0.8763		0.00 [-0.03, 0.04], 0.9664	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	1/48 (2.1)	0/24 (0.0)	2/47 (4.3)	0/24 (0.0)	3/95 (3.2)	0/48 (0.0)
RR [95%-CI]; p-value	1.02 [0.04, 29.38], 0.9904		2.09 [0.10, 44.48], 0.6379		3.06 [0.16, 59.94], 0.4606	
OR [95%-CI]; p-value	1.02 [0.03, 31.54], 0.9904		2.13 [0.09, 49.21], 0.6285		3.13 [0.15, 63.77], 0.4346	
RD [95%-CI]; p-value	0.00 [-0.07, 0.07], 0.9904		0.02 [-0.06, 0.10], 0.5893		0.02 [-0.02, 0.07], 0.3566	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.9647		0.3308		0.8165	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	26/43 (60.5)	19/26 (73.1)	27/53 (50.9)	7/20 (35.0)	53/96 (55.2)	26/46 (56.5)
RR [95%-CI]; p-value	0.83 [0.59, 1.16], 0.2690		1.46 [0.76, 2.80], 0.2599		0.98 [0.72, 1.33], 0.8822	
OR [95%-CI]; p-value	0.56 [0.20, 1.63], 0.2865		1.93 [0.66, 5.59], 0.2232		0.95 [0.47, 1.93], 0.8828	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.10], 0.2710		0.16 [-0.09, 0.41], 0.2088		-0.01 [-0.19, 0.16], 0.8827	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	28/50 (56.0)	14/22 (63.6)	20/44 (45.5)	16/28 (57.1)	48/94 (51.1)	30/50 (60.0)
RR [95%-CI]; p-value	0.88 [0.59, 1.31], 0.5313		0.80 [0.50, 1.25], 0.3250		0.85 [0.63, 1.15], 0.2931	
OR [95%-CI]; p-value	0.73 [0.26, 2.04], 0.5449		0.63 [0.24, 1.62], 0.3336		0.70 [0.35, 1.39], 0.3055	
RD [95%-CI]; p-value	-0.08 [-0.32, 0.17], 0.5389		-0.12 [-0.35, 0.12], 0.3297		-0.09 [-0.26, 0.08], 0.3008	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	28/48 (58.3)	17/24 (70.8)	23/47 (48.9)	12/24 (50.0)	51/95 (53.7)	29/48 (60.4)
RR [95%-CI]; p-value	0.82 [0.58, 1.17], 0.2780		0.98 [0.60, 1.61], 0.9322		0.89 [0.66, 1.19], 0.4333	
OR [95%-CI]; p-value	0.58 [0.20, 1.65], 0.3017		0.96 [0.36, 2.56], 0.9324		0.76 [0.38, 1.54], 0.4438	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.10], 0.2850		-0.01 [-0.26, 0.24], 0.9324		-0.07 [-0.24, 0.10], 0.4399	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.6864		0.5150		0.3321	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	13/43 (30.2)	10/26 (38.5)	14/53 (26.4)	4/20 (20.0)	27/96 (28.1)	14/46 (30.4)
RR [95%-CI]; p-value	0.79 [0.40, 1.53], 0.4782		1.32 [0.49, 3.54], 0.5799		0.92 [0.54, 1.59], 0.7751	
OR [95%-CI]; p-value	0.69 [0.25, 1.93], 0.4823		1.44 [0.41, 5.03], 0.5706		0.89 [0.41, 1.93], 0.7762	
RD [95%-CI]; p-value	-0.08 [-0.31, 0.15], 0.4869		0.06 [-0.15, 0.28], 0.5526		-0.02 [-0.18, 0.14], 0.7779	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	20/50 (40.0)	8/22 (36.4)	16/44 (36.4)	5/28 (17.9)	36/94 (38.3)	13/50 (26.0)
RR [95%-CI]; p-value	1.10 [0.57, 2.10], 0.7734		2.04 [0.84, 4.94], 0.1154		1.47 [0.86, 2.51], 0.1547	
OR [95%-CI]; p-value	1.17 [0.41, 3.29], 0.7706		2.63 [0.84, 8.27], 0.0921		1.77 [0.83, 3.76], 0.1381	
RD [95%-CI]; p-value	0.04 [-0.21, 0.28], 0.7689		0.19 [-0.02, 0.39], 0.0709		0.12 [-0.03, 0.28], 0.1231	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	17/48 (35.4)	11/24 (45.8)	19/47 (40.4)	9/24 (37.5)	36/95 (37.9)	20/48 (41.7)
RR [95%-CI]; p-value	0.77 [0.43, 1.38], 0.3827		1.08 [0.58, 2.01], 0.8130		0.91 [0.60, 1.39], 0.6596	
OR [95%-CI]; p-value	0.65 [0.24, 1.76], 0.3927		1.13 [0.41, 3.11], 0.8114		0.85 [0.42, 1.73], 0.6626	
RD [95%-CI]; p-value	-0.10 [-0.35, 0.14], 0.3968		0.03 [-0.21, 0.27], 0.8105		-0.04 [-0.21, 0.13], 0.6640	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s6
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.4972		0.4441		0.2234	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	3/26 (11.5)	2/53 (3.8)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.81 [0.20, 3.32], 0.7655		0.38 [0.06, 2.50], 0.3125		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.79 [0.16, 3.83], 0.7656		0.35 [0.05, 2.69], 0.2972		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.13], 0.7707		-0.06 [-0.20, 0.08], 0.3872		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	0/22 (0.0)	5/44 (11.4)	2/28 (7.1)	11/94 (11.7)	2/50 (4.0)
RR [95%-CI]; p-value	5.40 [0.31, 92.59], 0.2448		1.59 [0.33, 7.65], 0.5621		2.93 [0.67, 12.69], 0.1515	
OR [95%-CI]; p-value	6.00 [0.32, 112.37], 0.1776		1.67 [0.30, 9.25], 0.5556		3.18 [0.68, 14.96], 0.1247	
RD [95%-CI]; p-value	0.10 [-0.01, 0.21], 0.0780		0.04 [-0.09, 0.18], 0.5363		0.08 [-0.01, 0.16], 0.0747	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	3/24 (12.5)	3/47 (6.4)	3/24 (12.5)	11/95 (11.6)	6/48 (12.5)
RR [95%-CI]; p-value	1.33 [0.39, 4.58], 0.6475		0.51 [0.11, 2.34], 0.3870		0.93 [0.36, 2.35], 0.8722	
OR [95%-CI]; p-value	1.40 [0.34, 5.84], 0.6432		0.48 [0.09, 2.57], 0.3807		0.92 [0.32, 2.65], 0.8723	
RD [95%-CI]; p-value	0.04 [-0.13, 0.21], 0.6293		-0.06 [-0.21, 0.09], 0.4230		-0.01 [-0.12, 0.10], 0.8737	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_3_1_m_sf_ttl_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7392		0.6985		0.6210	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	3/26 (11.5)	4/53 (7.5)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.40 [0.07, 2.25], 0.3010		0.75 [0.15, 3.80], 0.7331		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.37 [0.06, 2.40], 0.2849		0.73 [0.12, 4.36], 0.7336		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3280		-0.02 [-0.17, 0.12], 0.7477		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	4/22 (18.2)	3/44 (6.8)	1/28 (3.6)	8/94 (8.5)	5/50 (10.0)
RR [95%-CI]; p-value	0.55 [0.16, 1.85], 0.3350		1.91 [0.21, 17.46], 0.5669		0.85 [0.29, 2.46], 0.7663	
OR [95%-CI]; p-value	0.50 [0.12, 2.08], 0.3336		1.98 [0.20, 20.00], 0.5577		0.84 [0.26, 2.71], 0.7665	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3766		0.03 [-0.07, 0.13], 0.5301		-0.01 [-0.12, 0.09], 0.7714	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	2/24 (8.3)	4/47 (8.5)	1/24 (4.2)	8/95 (8.4)	3/48 (6.3)
RR [95%-CI]; p-value	1.00 [0.20, 5.08], 1.0000		2.04 [0.24, 17.28], 0.5121		1.35 [0.37, 4.85], 0.6482	
OR [95%-CI]; p-value	1.00 [0.17, 5.89], 1.0000		2.14 [0.23, 20.28], 0.4986		1.38 [0.35, 5.45], 0.6455	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		0.04 [-0.07, 0.16], 0.4509		0.02 [-0.07, 0.11], 0.6301	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.7018		0.7377		0.7083	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	10/43 (23.3)	8/26 (30.8)	9/53 (17.0)	1/20 (5.0)	19/96 (19.8)	9/46 (19.6)
RR [95%-CI]; p-value	0.76 [0.34, 1.67], 0.4884		3.40 [0.46, 25.12], 0.2311		1.01 [0.50, 2.06], 0.9747	
OR [95%-CI]; p-value	0.68 [0.23, 2.03], 0.4910		3.89 [0.46, 32.86], 0.1842		1.01 [0.42, 2.46], 0.9747	
RD [95%-CI]; p-value	-0.08 [-0.29, 0.14], 0.4989		0.12 [-0.02, 0.26], 0.0913		0.00 [-0.14, 0.14], 0.9746	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	9/50 (18.0)	4/22 (18.2)	6/44 (13.6)	2/28 (7.1)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	0.99 [0.34, 2.87], 0.9853		1.91 [0.41, 8.80], 0.4070		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	0.99 [0.27, 3.63], 0.9853		2.05 [0.38, 10.97], 0.3927		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	-0.00 [-0.19, 0.19], 0.9853		0.06 [-0.07, 0.20], 0.3606		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	8/24 (33.3)	11/47 (23.4)	4/24 (16.7)	20/95 (21.1)	12/48 (25.0)
RR [95%-CI]; p-value	0.56 [0.25, 1.27], 0.1673		1.40 [0.50, 3.95], 0.5196		0.84 [0.45, 1.57], 0.5905	
OR [95%-CI]; p-value	0.46 [0.15, 1.41], 0.1696		1.53 [0.43, 5.43], 0.5106		0.80 [0.35, 1.81], 0.5928	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.07], 0.1909		0.07 [-0.12, 0.26], 0.4917		-0.04 [-0.19, 0.11], 0.5997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.3480		0.4449		0.1769	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	7/26 (26.9)	5/53 (9.4)	3/20 (15.0)	9/96 (9.4)	10/46 (21.7)
RR [95%-CI]; p-value	0.35 [0.11, 1.07], 0.0648		0.63 [0.17, 2.39], 0.4962		0.43 [0.19, 0.99], 0.0468	
OR [95%-CI]; p-value	0.28 [0.07, 1.07], 0.0527		0.59 [0.13, 2.74], 0.4971		0.37 [0.14, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.18 [-0.37, 0.02], 0.0711		-0.06 [-0.23, 0.12], 0.5334		-0.12 [-0.26, 0.01], 0.0678	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	8/50 (16.0)	3/22 (13.6)	7/44 (15.9)	3/28 (10.7)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	1.17 [0.34, 4.01], 0.7987		1.48 [0.42, 5.27], 0.5408		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	1.21 [0.29, 5.06], 0.7973		1.58 [0.37, 6.68], 0.5344		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7921		0.05 [-0.11, 0.21], 0.5180		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	5/24 (20.8)	5/47 (10.6)	5/24 (20.8)	12/95 (12.6)	10/48 (20.8)
RR [95%-CI]; p-value	0.70 [0.25, 1.98], 0.5006		0.51 [0.16, 1.59], 0.2470		0.61 [0.28, 1.30], 0.1993	
OR [95%-CI]; p-value	0.65 [0.18, 2.31], 0.5023		0.45 [0.12, 1.75], 0.2427		0.55 [0.22, 1.38], 0.1993	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5206		-0.10 [-0.29, 0.08], 0.2797		-0.08 [-0.21, 0.05], 0.2264	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2110		0.5244		0.7191	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	6/26 (23.1)	11/53 (20.8)	3/20 (15.0)	22/96 (22.9)	9/46 (19.6)
RR [95%-CI]; p-value	1.11 [0.47, 2.64], 0.8159		1.38 [0.43, 4.45], 0.5859		1.17 [0.59, 2.34], 0.6540	
OR [95%-CI]; p-value	1.15 [0.37, 3.59], 0.8150		1.48 [0.37, 5.99], 0.5775		1.22 [0.51, 2.92], 0.6510	
RD [95%-CI]; p-value	0.03 [-0.18, 0.23], 0.8134		0.06 [-0.13, 0.25], 0.5545		0.03 [-0.11, 0.18], 0.6440	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	17/50 (34.0)	5/22 (22.7)	9/44 (20.5)	8/28 (28.6)	26/94 (27.7)	13/50 (26.0)
RR [95%-CI]; p-value	1.50 [0.63, 3.54], 0.3597		0.72 [0.31, 1.64], 0.4279		1.06 [0.60, 1.88], 0.8317	
OR [95%-CI]; p-value	1.75 [0.55, 5.57], 0.3388		0.64 [0.21, 1.93], 0.4292		1.09 [0.50, 2.37], 0.8311	
RD [95%-CI]; p-value	0.11 [-0.11, 0.33], 0.3128		-0.08 [-0.29, 0.12], 0.4387		0.02 [-0.13, 0.17], 0.8300	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	9/24 (37.5)	13/47 (27.7)	5/24 (20.8)	23/95 (24.2)	14/48 (29.2)
RR [95%-CI]; p-value	0.56 [0.26, 1.18], 0.1273		1.33 [0.54, 3.29], 0.5401		0.83 [0.47, 1.46], 0.5194	
OR [95%-CI]; p-value	0.44 [0.15, 1.29], 0.1304		1.45 [0.45, 4.70], 0.5317		0.78 [0.36, 1.69], 0.5228	
RD [95%-CI]; p-value	-0.17 [-0.39, 0.06], 0.1469		0.07 [-0.14, 0.28], 0.5176		-0.05 [-0.20, 0.11], 0.5302	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.3456		0.5882		0.6032	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	7/96 (7.3)	3/46 (6.5)
RR [95%-CI]; p-value	1.51 [0.32, 7.24], 0.6050		0.75 [0.07, 7.87], 0.8140		1.12 [0.30, 4.13], 0.8670	
OR [95%-CI]; p-value	1.58 [0.28, 8.80], 0.5998		0.75 [0.06, 8.70], 0.8139		1.13 [0.28, 4.57], 0.8667	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5823		-0.01 [-0.12, 0.10], 0.8245		0.01 [-0.08, 0.10], 0.8643	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	3/22 (13.6)	4/44 (9.1)	0/28 (0.0)	9/94 (9.6)	3/50 (6.0)
RR [95%-CI]; p-value	0.73 [0.19, 2.80], 0.6502		5.18 [0.28, 94.36], 0.2665		1.60 [0.45, 5.63], 0.4675	
OR [95%-CI]; p-value	0.70 [0.15, 3.24], 0.6511		5.60 [0.28, 110.18], 0.2060		1.66 [0.43, 6.43], 0.4600	
RD [95%-CI]; p-value	-0.04 [-0.20, 0.13], 0.6672		0.07 [-0.02, 0.17], 0.1409		0.04 [-0.05, 0.12], 0.4297	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	0/24 (0.0)	5/47 (10.6)	2/24 (8.3)	12/95 (12.6)	2/48 (4.2)
RR [95%-CI]; p-value	7.15 [0.42, 120.79], 0.1728		1.28 [0.27, 6.10], 0.7596		3.03 [0.71, 13.00], 0.1355	
OR [95%-CI]; p-value	8.20 [0.45, 150.89], 0.0972		1.31 [0.23, 7.31], 0.7579		3.33 [0.71, 15.51], 0.1077	
RD [95%-CI]; p-value	0.13 [0.01, 0.24], 0.0318		0.02 [-0.12, 0.16], 0.7494		0.08 [-0.00, 0.17], 0.0580	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.4574		0.7323		0.4402	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	4/26 (15.4)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	6/46 (13.0)
RR [95%-CI]; p-value	0.45 [0.11, 1.87], 0.2736		0.94 [0.20, 4.48], 0.9415		0.64 [0.24, 1.73], 0.3791	
OR [95%-CI]; p-value	0.41 [0.08, 2.01], 0.2623		0.94 [0.17, 5.27], 0.9416		0.61 [0.20, 1.86], 0.3783	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2976		-0.01 [-0.16, 0.15], 0.9423		-0.05 [-0.16, 0.06], 0.4095	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	1/22 (4.5)	5/44 (11.4)	2/28 (7.1)	10/94 (10.6)	3/50 (6.0)
RR [95%-CI]; p-value	2.20 [0.27, 17.75], 0.4592		1.59 [0.33, 7.65], 0.5621		1.77 [0.51, 6.15], 0.3668	
OR [95%-CI]; p-value	2.33 [0.26, 21.24], 0.4405		1.67 [0.30, 9.25], 0.5556		1.87 [0.49, 7.11], 0.3551	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3745		0.04 [-0.09, 0.18], 0.5363		0.05 [-0.04, 0.14], 0.3160	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	13/95 (13.7)	8/48 (16.7)
RR [95%-CI]; p-value	0.90 [0.34, 2.39], 0.8326		0.68 [0.17, 2.80], 0.5941		0.82 [0.37, 1.84], 0.6331	
OR [95%-CI]; p-value	0.88 [0.26, 2.98], 0.8332		0.65 [0.13, 3.18], 0.5938		0.79 [0.30, 2.07], 0.6342	
RD [95%-CI]; p-value	-0.02 [-0.22, 0.18], 0.8353		-0.04 [-0.19, 0.11], 0.6128		-0.03 [-0.16, 0.10], 0.6429	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.2418		0.4047		0.4582	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	9/26 (34.6)	8/53 (15.1)	2/20 (10.0)	13/96 (13.5)	11/46 (23.9)
RR [95%-CI]; p-value	0.34 [0.13, 0.89], 0.0289		1.51 [0.35, 6.51], 0.5809		0.57 [0.28, 1.17], 0.1226	
OR [95%-CI]; p-value	0.25 [0.07, 0.85], 0.0214		1.60 [0.31, 8.27], 0.5724		0.50 [0.20, 1.22], 0.1228	
RD [95%-CI]; p-value	-0.23 [-0.44, -0.02], 0.0291		0.05 [-0.11, 0.21], 0.5402		-0.10 [-0.24, 0.04], 0.1494	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	13/50 (26.0)	7/22 (31.8)	7/44 (15.9)	3/28 (10.7)	20/94 (21.3)	10/50 (20.0)
RR [95%-CI]; p-value	0.82 [0.38, 1.76], 0.6072		1.48 [0.42, 5.27], 0.5408		1.06 [0.54, 2.09], 0.8579	
OR [95%-CI]; p-value	0.75 [0.25, 2.26], 0.6116		1.58 [0.37, 6.68], 0.5344		1.08 [0.46, 2.53], 0.8575	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.17], 0.6192		0.05 [-0.11, 0.21], 0.5180		0.01 [-0.13, 0.15], 0.8565	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	5/24 (20.8)	10/47 (21.3)	8/24 (33.3)	20/95 (21.1)	13/48 (27.1)
RR [95%-CI]; p-value	1.00 [0.38, 2.60], 1.0000		0.64 [0.29, 1.41], 0.2648		0.78 [0.42, 1.42], 0.4152	
OR [95%-CI]; p-value	1.00 [0.30, 3.34], 1.0000		0.54 [0.18, 1.62], 0.2693		0.72 [0.32, 1.61], 0.4189	
RD [95%-CI]; p-value	0.00 [-0.20, 0.20], 1.0000		-0.12 [-0.34, 0.10], 0.2870		-0.06 [-0.21, 0.09], 0.4310	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3193		0.1824		0.0755	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	8/26 (30.8)	13/53 (24.5)	3/20 (15.0)	24/96 (25.0)	11/46 (23.9)
RR [95%-CI]; p-value	0.83 [0.39, 1.79], 0.6382		1.64 [0.52, 5.14], 0.4000		1.05 [0.56, 1.95], 0.8884	
OR [95%-CI]; p-value	0.77 [0.26, 2.27], 0.6402		1.84 [0.46, 7.30], 0.3801		1.06 [0.47, 2.41], 0.8881	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.17], 0.6442		0.10 [-0.10, 0.29], 0.3375		0.01 [-0.14, 0.16], 0.8875	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	7/22 (31.8)	4/44 (9.1)	7/28 (25.0)	9/94 (9.6)	14/50 (28.0)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		0.36 [0.12, 1.13], 0.0802		0.34 [0.16, 0.73], 0.0059	
OR [95%-CI]; p-value	0.24 [0.07, 0.86], 0.0221		0.30 [0.08, 1.14], 0.0674		0.27 [0.11, 0.69], 0.0041	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0433		-0.16 [-0.34, 0.02], 0.0858		-0.18 [-0.32, -0.05], 0.0088	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	8/24 (33.3)	5/47 (10.6)	4/24 (16.7)	13/95 (13.7)	12/48 (25.0)
RR [95%-CI]; p-value	0.50 [0.21, 1.17], 0.1094		0.64 [0.19, 2.16], 0.4705		0.55 [0.27, 1.11], 0.0932	
OR [95%-CI]; p-value	0.40 [0.13, 1.25], 0.1088		0.60 [0.14, 2.46], 0.4702		0.48 [0.20, 1.14], 0.0925	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.05], 0.1306		-0.06 [-0.23, 0.11], 0.4951		-0.11 [-0.25, 0.03], 0.1148	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.6254		0.6749		0.5805	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	4/26 (15.4)	5/53 (9.4)	0/20 (0.0)	10/96 (10.4)	4/46 (8.7)
RR [95%-CI]; p-value	0.76 [0.22, 2.56], 0.6532		3.87 [0.22, 67.68], 0.3543		1.20 [0.40, 3.62], 0.7487	
OR [95%-CI]; p-value	0.72 [0.18, 2.98], 0.6534		4.17 [0.22, 79.89], 0.3067		1.22 [0.36, 4.12], 0.7475	
RD [95%-CI]; p-value	-0.04 [-0.21, 0.13], 0.6622		0.07 [-0.03, 0.17], 0.1841		0.02 [-0.08, 0.12], 0.7404	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	6/22 (27.3)	6/44 (13.6)	4/28 (14.3)	11/94 (11.7)	10/50 (20.0)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0675		0.95 [0.30, 3.09], 0.9380		0.59 [0.27, 1.28], 0.1806	
OR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0606		0.95 [0.24, 3.71], 0.9381		0.53 [0.21, 1.35], 0.1792	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.03], 0.0967		-0.01 [-0.17, 0.16], 0.9384		-0.08 [-0.21, 0.05], 0.2057	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	3/24 (12.5)	9/47 (19.1)	4/24 (16.7)	11/95 (11.6)	7/48 (14.6)
RR [95%-CI]; p-value	0.33 [0.06, 1.86], 0.2108		1.15 [0.39, 3.35], 0.7993		0.79 [0.33, 1.92], 0.6081	
OR [95%-CI]; p-value	0.30 [0.05, 1.96], 0.1898		1.18 [0.32, 4.33], 0.7981		0.77 [0.28, 2.12], 0.6090	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2563		0.02 [-0.16, 0.21], 0.7945		-0.03 [-0.15, 0.09], 0.6201	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.0820		0.3690		0.2977	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	6/26 (23.1)	8/53 (15.1)	0/20 (0.0)	11/96 (11.5)	6/46 (13.0)
RR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0708		6.19 [0.37, 102.92], 0.2038		0.88 [0.35, 2.23], 0.7849	
OR [95%-CI]; p-value	0.25 [0.06, 1.11], 0.0543		7.11 [0.39, 129.92], 0.1281		0.86 [0.30, 2.50], 0.7854	
RD [95%-CI]; p-value	-0.16 [-0.34, 0.02], 0.0778		0.13 [0.01, 0.24], 0.0344		-0.02 [-0.13, 0.10], 0.7894	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	10/50 (20.0)	1/22 (4.5)	5/44 (11.4)	4/28 (14.3)	15/94 (16.0)	5/50 (10.0)
RR [95%-CI]; p-value	4.40 [0.60, 32.30], 0.1452		0.80 [0.23, 2.71], 0.7146		1.60 [0.62, 4.14], 0.3361	
OR [95%-CI]; p-value	5.25 [0.63, 43.84], 0.0931		0.77 [0.19, 3.15], 0.7147		1.71 [0.58, 5.01], 0.3250	
RD [95%-CI]; p-value	0.15 [0.01, 0.30], 0.0316		-0.03 [-0.19, 0.13], 0.7203		0.06 [-0.05, 0.17], 0.2943	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	9/95 (9.5)	8/48 (16.7)
RR [95%-CI]; p-value	0.50 [0.16, 1.56], 0.2328		0.68 [0.17, 2.80], 0.5941		0.57 [0.23, 1.38], 0.2119	
OR [95%-CI]; p-value	0.44 [0.11, 1.71], 0.2283		0.65 [0.13, 3.18], 0.5938		0.52 [0.19, 1.46], 0.2095	
RD [95%-CI]; p-value	-0.10 [-0.29, 0.08], 0.2673		-0.04 [-0.19, 0.11], 0.6128		-0.07 [-0.19, 0.05], 0.2430	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.6188		0.5596		0.3177	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	5/26 (19.2)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	7/46 (15.2)
RR [95%-CI]; p-value	0.36 [0.09, 1.39], 0.1398		0.94 [0.20, 4.48], 0.9415		0.55 [0.21, 1.42], 0.2148	
OR [95%-CI]; p-value	0.32 [0.07, 1.45], 0.1234		0.94 [0.17, 5.27], 0.9416		0.51 [0.17, 1.49], 0.2117	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1566		-0.01 [-0.16, 0.15], 0.9423		-0.07 [-0.19, 0.05], 0.2513	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	1/22 (4.5)	5/44 (11.4)	1/28 (3.6)	8/94 (8.5)	2/50 (4.0)
RR [95%-CI]; p-value	1.32 [0.15, 12.00], 0.8052		3.18 [0.39, 25.83], 0.2787		2.13 [0.47, 9.64], 0.3274	
OR [95%-CI]; p-value	1.34 [0.13, 13.65], 0.8040		3.46 [0.38, 31.32], 0.2435		2.23 [0.46, 10.94], 0.3107	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.7939		0.08 [-0.04, 0.19], 0.1890		0.05 [-0.03, 0.12], 0.2589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	3/24 (12.5)	5/47 (10.6)	3/24 (12.5)	8/95 (8.4)	6/48 (12.5)
RR [95%-CI]; p-value	0.50 [0.11, 2.29], 0.3725		0.85 [0.22, 3.26], 0.8141		0.67 [0.25, 1.83], 0.4388	
OR [95%-CI]; p-value	0.47 [0.09, 2.51], 0.3657		0.83 [0.18, 3.83], 0.8145		0.64 [0.21, 1.97], 0.4383	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4109		-0.02 [-0.18, 0.14], 0.8185		-0.04 [-0.15, 0.07], 0.4631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.1.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4917		0.1687		0.4286	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	4/26 (15.4)	2/53 (3.8)	1/20 (5.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.60 [0.17, 2.21], 0.4473		0.75 [0.07, 7.87], 0.8140		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.56 [0.13, 2.48], 0.4444		0.75 [0.06, 8.70], 0.8139		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.10], 0.4663		-0.01 [-0.12, 0.10], 0.8245		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	4/22 (18.2)	5/44 (11.4)	0/28 (0.0)	11/94 (11.7)	4/50 (8.0)
RR [95%-CI]; p-value	0.66 [0.21, 2.11], 0.4832		6.48 [0.37, 114.08], 0.2018		1.46 [0.49, 4.36], 0.4947	
OR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4847		7.18 [0.38, 136.81], 0.1312		1.52 [0.46, 5.06], 0.4887	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5117		0.10 [-0.01, 0.20], 0.0741		0.04 [-0.06, 0.14], 0.4653	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	1/24 (4.2)	4/47 (8.5)	6/24 (25.0)	9/95 (9.5)	7/48 (14.6)
RR [95%-CI]; p-value	2.50 [0.31, 20.22], 0.3903		0.34 [0.11, 1.09], 0.0700		0.65 [0.26, 1.64], 0.3606	
OR [95%-CI]; p-value	2.67 [0.29, 24.28], 0.3657		0.28 [0.07, 1.11], 0.0588		0.61 [0.21, 1.76], 0.3600	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.2981		-0.16 [-0.36, 0.03], 0.0902		-0.05 [-0.17, 0.06], 0.3876	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_1_m_soc_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.3.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8658		0.9155		0.6005	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	6/26 (23.1)	2/53 (3.8)	0/20 (0.0)	4/96 (4.2)	6/46 (13.0)
RR [95%-CI]; p-value	0.20 [0.04, 0.93], 0.0395		1.55 [0.07, 32.89], 0.7796		0.32 [0.09, 1.08], 0.0657	
OR [95%-CI]; p-value	0.16 [0.03, 0.88], 0.0205		1.57 [0.07, 36.31], 0.7771		0.29 [0.08, 1.08], 0.0530	
RD [95%-CI]; p-value	-0.18 [-0.36, -0.01], 0.0377		0.01 [-0.07, 0.10], 0.7561		-0.09 [-0.19, 0.02], 0.0982	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	1/50 (2.0)	1/22 (4.5)	1/44 (2.3)	0/28 (0.0)	2/94 (2.1)	1/50 (2.0)
RR [95%-CI]; p-value	0.44 [0.03, 6.72], 0.5550		1.30 [0.04, 37.37], 0.8800		1.06 [0.10, 11.45], 0.9593	
OR [95%-CI]; p-value	0.43 [0.03, 7.18], 0.5449		1.30 [0.04, 40.13], 0.8796		1.07 [0.09, 12.04], 0.9593	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.6006		0.01 [-0.06, 0.07], 0.8763		0.00 [-0.05, 0.05], 0.9589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	6/95 (6.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.30 [0.08, 1.15], 0.0793		3.13 [0.16, 59.98], 0.4493		0.61 [0.19, 1.89], 0.3875	
OR [95%-CI]; p-value	0.25 [0.05, 1.17], 0.0634		3.27 [0.16, 68.07], 0.4193		0.58 [0.17, 2.01], 0.3848	
RD [95%-CI]; p-value	-0.15 [-0.32, 0.03], 0.1050		0.04 [-0.05, 0.13], 0.3419		-0.04 [-0.14, 0.06], 0.4183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_3_m_pt_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.3.s6
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4268		0.4688		0.4917	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	2/53 (3.8)	0/20 (0.0)	5/96 (5.2)	2/46 (4.3)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		1.55 [0.07, 32.89], 0.7796		1.20 [0.24, 5.94], 0.8251	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		1.57 [0.07, 36.31], 0.7771		1.21 [0.23, 6.48], 0.8246	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		0.01 [-0.07, 0.10], 0.7561		0.01 [-0.07, 0.08], 0.8193	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	3/22 (13.6)	2/44 (4.5)	3/28 (10.7)	4/94 (4.3)	6/50 (12.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.63], 0.1616		0.42 [0.08, 2.38], 0.3300		0.35 [0.10, 1.20], 0.0952	
OR [95%-CI]; p-value	0.26 [0.04, 1.71], 0.1384		0.40 [0.06, 2.54], 0.3155		0.33 [0.09, 1.21], 0.0818	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.06], 0.2181		-0.06 [-0.19, 0.07], 0.3525		-0.08 [-0.18, 0.02], 0.1248	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	5/95 (5.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.20 [0.04, 0.96], 0.0438		3.13 [0.16, 59.98], 0.4493		0.51 [0.15, 1.66], 0.2609	
OR [95%-CI]; p-value	0.17 [0.03, 0.93], 0.0244		3.27 [0.16, 68.07], 0.4193		0.48 [0.13, 1.74], 0.2538	
RD [95%-CI]; p-value	-0.17 [-0.34, 0.01], 0.0576		0.04 [-0.05, 0.13], 0.3419		-0.05 [-0.15, 0.05], 0.2997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_3_m_pt_ae10pct_ttlpth.sas using SAS 9.4

Table 12.4.8.1.1.s6
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.8157		0.9303		0.8122	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	1/53 (1.9)	0/20 (0.0)	4/96 (4.2)	2/46 (4.3)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		0.77 [0.03, 22.19], 0.8808		0.96 [0.18, 5.04], 0.9599	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		0.77 [0.02, 23.84], 0.8806		0.96 [0.17, 5.42], 0.9599	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		-0.01 [-0.08, 0.07], 0.8870		-0.00 [-0.07, 0.07], 0.9602	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	0/22 (0.0)	3/44 (6.8)	2/28 (7.1)	6/94 (6.4)	2/50 (4.0)
RR [95%-CI]; p-value	2.70 [0.14, 51.70], 0.5096		0.95 [0.17, 5.36], 0.9579		1.60 [0.33, 7.62], 0.5579	
OR [95%-CI]; p-value	2.81 [0.13, 58.50], 0.4875		0.95 [0.15, 6.08], 0.9579		1.64 [0.32, 8.42], 0.5523	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4090		-0.00 [-0.12, 0.12], 0.9581		0.02 [-0.05, 0.10], 0.5248	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	1/24 (4.2)	1/47 (2.1)	1/24 (4.2)	3/95 (3.2)	2/48 (4.2)
RR [95%-CI]; p-value	1.00 [0.10, 10.48], 1.0000		0.51 [0.03, 7.81], 0.6292		0.76 [0.13, 4.38], 0.7569	
OR [95%-CI]; p-value	1.00 [0.09, 11.61], 1.0000		0.50 [0.03, 8.36], 0.6233		0.75 [0.12, 4.65], 0.7565	
RD [95%-CI]; p-value	0.00 [-0.10, 0.10], 1.0000		-0.02 [-0.11, 0.07], 0.6569		-0.01 [-0.08, 0.06], 0.7665	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_8_1_1_m_soc_sae5pct_ttlpth.sas using SAS 9.4

Table 12.4.8.1.2.s6
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_8_1_2_m_pt_sae5pct_ttlpth.sas using SAS 9.4

Table 12.4.5.1.1.s6
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_5_1_1_m_soc_aeg35pct_ttlpth.sas using SAS 9.4

Table 12.4.5.1.2.s6
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_5_1_2_m_pt_aeg35pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.7392		0.6985		0.6210	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	3/26 (11.5)	4/53 (7.5)	2/20 (10.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.40 [0.07, 2.25], 0.3010		0.75 [0.15, 3.80], 0.7331		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.37 [0.06, 2.40], 0.2849		0.73 [0.12, 4.36], 0.7336		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3280		-0.02 [-0.17, 0.12], 0.7477		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	4/22 (18.2)	3/44 (6.8)	1/28 (3.6)	8/94 (8.5)	5/50 (10.0)
RR [95%-CI]; p-value	0.55 [0.16, 1.85], 0.3350		1.91 [0.21, 17.46], 0.5669		0.85 [0.29, 2.46], 0.7663	
OR [95%-CI]; p-value	0.50 [0.12, 2.08], 0.3336		1.98 [0.20, 20.00], 0.5577		0.84 [0.26, 2.71], 0.7665	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3766		0.03 [-0.07, 0.13], 0.5301		-0.01 [-0.12, 0.09], 0.7714	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	2/24 (8.3)	4/47 (8.5)	1/24 (4.2)	8/95 (8.4)	3/48 (6.3)
RR [95%-CI]; p-value	1.00 [0.20, 5.08], 1.0000		2.04 [0.24, 17.28], 0.5121		1.35 [0.37, 4.85], 0.6482	
OR [95%-CI]; p-value	1.00 [0.17, 5.89], 1.0000		2.14 [0.23, 20.28], 0.4986		1.38 [0.35, 5.45], 0.6455	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		0.04 [-0.07, 0.16], 0.4509		0.02 [-0.07, 0.11], 0.6301	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.7018		0.7377		0.7083	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	10/43 (23.3)	8/26 (30.8)	9/53 (17.0)	1/20 (5.0)	19/96 (19.8)	9/46 (19.6)
RR [95%-CI]; p-value	0.76 [0.34, 1.67], 0.4884		3.40 [0.46, 25.12], 0.2311		1.01 [0.50, 2.06], 0.9747	
OR [95%-CI]; p-value	0.68 [0.23, 2.03], 0.4910		3.89 [0.46, 32.86], 0.1842		1.01 [0.42, 2.46], 0.9747	
RD [95%-CI]; p-value	-0.08 [-0.29, 0.14], 0.4989		0.12 [-0.02, 0.26], 0.0913		0.00 [-0.14, 0.14], 0.9746	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	9/50 (18.0)	4/22 (18.2)	6/44 (13.6)	2/28 (7.1)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	0.99 [0.34, 2.87], 0.9853		1.91 [0.41, 8.80], 0.4070		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	0.99 [0.27, 3.63], 0.9853		2.05 [0.38, 10.97], 0.3927		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	-0.00 [-0.19, 0.19], 0.9853		0.06 [-0.07, 0.20], 0.3606		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	8/24 (33.3)	11/47 (23.4)	4/24 (16.7)	20/95 (21.1)	12/48 (25.0)
RR [95%-CI]; p-value	0.56 [0.25, 1.27], 0.1673		1.40 [0.50, 3.95], 0.5196		0.84 [0.45, 1.57], 0.5905	
OR [95%-CI]; p-value	0.46 [0.15, 1.41], 0.1696		1.53 [0.43, 5.43], 0.5106		0.80 [0.35, 1.81], 0.5928	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.07], 0.1909		0.07 [-0.12, 0.26], 0.4917		-0.04 [-0.19, 0.11], 0.5997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.3480		0.4449		0.1769	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	7/26 (26.9)	5/53 (9.4)	3/20 (15.0)	9/96 (9.4)	10/46 (21.7)
RR [95%-CI]; p-value	0.35 [0.11, 1.07], 0.0648		0.63 [0.17, 2.39], 0.4962		0.43 [0.19, 0.99], 0.0468	
OR [95%-CI]; p-value	0.28 [0.07, 1.07], 0.0527		0.59 [0.13, 2.74], 0.4971		0.37 [0.14, 0.99], 0.0428	
RD [95%-CI]; p-value	-0.18 [-0.37, 0.02], 0.0711		-0.06 [-0.23, 0.12], 0.5334		-0.12 [-0.26, 0.01], 0.0678	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	8/50 (16.0)	3/22 (13.6)	7/44 (15.9)	3/28 (10.7)	15/94 (16.0)	6/50 (12.0)
RR [95%-CI]; p-value	1.17 [0.34, 4.01], 0.7987		1.48 [0.42, 5.27], 0.5408		1.33 [0.55, 3.21], 0.5267	
OR [95%-CI]; p-value	1.21 [0.29, 5.06], 0.7973		1.58 [0.37, 6.68], 0.5344		1.39 [0.50, 3.85], 0.5218	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7921		0.05 [-0.11, 0.21], 0.5180		0.04 [-0.08, 0.16], 0.5059	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	5/24 (20.8)	5/47 (10.6)	5/24 (20.8)	12/95 (12.6)	10/48 (20.8)
RR [95%-CI]; p-value	0.70 [0.25, 1.98], 0.5006		0.51 [0.16, 1.59], 0.2470		0.61 [0.28, 1.30], 0.1993	
OR [95%-CI]; p-value	0.65 [0.18, 2.31], 0.5023		0.45 [0.12, 1.75], 0.2427		0.55 [0.22, 1.38], 0.1993	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5206		-0.10 [-0.29, 0.08], 0.2797		-0.08 [-0.21, 0.05], 0.2264	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2110		0.5244		0.7191	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	6/26 (23.1)	11/53 (20.8)	3/20 (15.0)	22/96 (22.9)	9/46 (19.6)
RR [95%-CI]; p-value	1.11 [0.47, 2.64], 0.8159		1.38 [0.43, 4.45], 0.5859		1.17 [0.59, 2.34], 0.6540	
OR [95%-CI]; p-value	1.15 [0.37, 3.59], 0.8150		1.48 [0.37, 5.99], 0.5775		1.22 [0.51, 2.92], 0.6510	
RD [95%-CI]; p-value	0.03 [-0.18, 0.23], 0.8134		0.06 [-0.13, 0.25], 0.5545		0.03 [-0.11, 0.18], 0.6440	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	17/50 (34.0)	5/22 (22.7)	9/44 (20.5)	8/28 (28.6)	26/94 (27.7)	13/50 (26.0)
RR [95%-CI]; p-value	1.50 [0.63, 3.54], 0.3597		0.72 [0.31, 1.64], 0.4279		1.06 [0.60, 1.88], 0.8317	
OR [95%-CI]; p-value	1.75 [0.55, 5.57], 0.3388		0.64 [0.21, 1.93], 0.4292		1.09 [0.50, 2.37], 0.8311	
RD [95%-CI]; p-value	0.11 [-0.11, 0.33], 0.3128		-0.08 [-0.29, 0.12], 0.4387		0.02 [-0.13, 0.17], 0.8300	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	9/24 (37.5)	13/47 (27.7)	5/24 (20.8)	23/95 (24.2)	14/48 (29.2)
RR [95%-CI]; p-value	0.56 [0.26, 1.18], 0.1273		1.33 [0.54, 3.29], 0.5401		0.83 [0.47, 1.46], 0.5194	
OR [95%-CI]; p-value	0.44 [0.15, 1.29], 0.1304		1.45 [0.45, 4.70], 0.5317		0.78 [0.36, 1.69], 0.5228	
RD [95%-CI]; p-value	-0.17 [-0.39, 0.06], 0.1469		0.07 [-0.14, 0.28], 0.5176		-0.05 [-0.20, 0.11], 0.5302	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.3456		0.5882		0.6032	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	7/96 (7.3)	3/46 (6.5)
RR [95%-CI]; p-value	1.51 [0.32, 7.24], 0.6050		0.75 [0.07, 7.87], 0.8140		1.12 [0.30, 4.13], 0.8670	
OR [95%-CI]; p-value	1.58 [0.28, 8.80], 0.5998		0.75 [0.06, 8.70], 0.8139		1.13 [0.28, 4.57], 0.8667	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5823		-0.01 [-0.12, 0.10], 0.8245		0.01 [-0.08, 0.10], 0.8643	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	3/22 (13.6)	4/44 (9.1)	0/28 (0.0)	9/94 (9.6)	3/50 (6.0)
RR [95%-CI]; p-value	0.73 [0.19, 2.80], 0.6502		5.18 [0.28, 94.36], 0.2665		1.60 [0.45, 5.63], 0.4675	
OR [95%-CI]; p-value	0.70 [0.15, 3.24], 0.6511		5.60 [0.28, 110.18], 0.2060		1.66 [0.43, 6.43], 0.4600	
RD [95%-CI]; p-value	-0.04 [-0.20, 0.13], 0.6672		0.07 [-0.02, 0.17], 0.1409		0.04 [-0.05, 0.12], 0.4297	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	7/48 (14.6)	0/24 (0.0)	5/47 (10.6)	2/24 (8.3)	12/95 (12.6)	2/48 (4.2)
RR [95%-CI]; p-value	7.15 [0.42, 120.79], 0.1728		1.28 [0.27, 6.10], 0.7596		3.03 [0.71, 13.00], 0.1355	
OR [95%-CI]; p-value	8.20 [0.45, 150.89], 0.0972		1.31 [0.23, 7.31], 0.7579		3.33 [0.71, 15.51], 0.1077	
RD [95%-CI]; p-value	0.13 [0.01, 0.24], 0.0318		0.02 [-0.12, 0.16], 0.7494		0.08 [-0.00, 0.17], 0.0580	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.4574		0.7323		0.4402	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	4/26 (15.4)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	6/46 (13.0)
RR [95%-CI]; p-value	0.45 [0.11, 1.87], 0.2736		0.94 [0.20, 4.48], 0.9415		0.64 [0.24, 1.73], 0.3791	
OR [95%-CI]; p-value	0.41 [0.08, 2.01], 0.2623		0.94 [0.17, 5.27], 0.9416		0.61 [0.20, 1.86], 0.3783	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2976		-0.01 [-0.16, 0.15], 0.9423		-0.05 [-0.16, 0.06], 0.4095	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	1/22 (4.5)	5/44 (11.4)	2/28 (7.1)	10/94 (10.6)	3/50 (6.0)
RR [95%-CI]; p-value	2.20 [0.27, 17.75], 0.4592		1.59 [0.33, 7.65], 0.5621		1.77 [0.51, 6.15], 0.3668	
OR [95%-CI]; p-value	2.33 [0.26, 21.24], 0.4405		1.67 [0.30, 9.25], 0.5556		1.87 [0.49, 7.11], 0.3551	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.3745		0.04 [-0.09, 0.18], 0.5363		0.05 [-0.04, 0.14], 0.3160	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	9/48 (18.8)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	13/95 (13.7)	8/48 (16.7)
RR [95%-CI]; p-value	0.90 [0.34, 2.39], 0.8326		0.68 [0.17, 2.80], 0.5941		0.82 [0.37, 1.84], 0.6331	
OR [95%-CI]; p-value	0.88 [0.26, 2.98], 0.8332		0.65 [0.13, 3.18], 0.5938		0.79 [0.30, 2.07], 0.6342	
RD [95%-CI]; p-value	-0.02 [-0.22, 0.18], 0.8353		-0.04 [-0.19, 0.11], 0.6128		-0.03 [-0.16, 0.10], 0.6429	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.2418		0.4047		0.4582	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	9/26 (34.6)	8/53 (15.1)	2/20 (10.0)	13/96 (13.5)	11/46 (23.9)
RR [95%-CI]; p-value	0.34 [0.13, 0.89], 0.0289		1.51 [0.35, 6.51], 0.5809		0.57 [0.28, 1.17], 0.1226	
OR [95%-CI]; p-value	0.25 [0.07, 0.85], 0.0214		1.60 [0.31, 8.27], 0.5724		0.50 [0.20, 1.22], 0.1228	
RD [95%-CI]; p-value	-0.23 [-0.44, -0.02], 0.0291		0.05 [-0.11, 0.21], 0.5402		-0.10 [-0.24, 0.04], 0.1494	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	13/50 (26.0)	7/22 (31.8)	7/44 (15.9)	3/28 (10.7)	20/94 (21.3)	10/50 (20.0)
RR [95%-CI]; p-value	0.82 [0.38, 1.76], 0.6072		1.48 [0.42, 5.27], 0.5408		1.06 [0.54, 2.09], 0.8579	
OR [95%-CI]; p-value	0.75 [0.25, 2.26], 0.6116		1.58 [0.37, 6.68], 0.5344		1.08 [0.46, 2.53], 0.8575	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.17], 0.6192		0.05 [-0.11, 0.21], 0.5180		0.01 [-0.13, 0.15], 0.8565	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	5/24 (20.8)	10/47 (21.3)	8/24 (33.3)	20/95 (21.1)	13/48 (27.1)
RR [95%-CI]; p-value	1.00 [0.38, 2.60], 1.0000		0.64 [0.29, 1.41], 0.2648		0.78 [0.42, 1.42], 0.4152	
OR [95%-CI]; p-value	1.00 [0.30, 3.34], 1.0000		0.54 [0.18, 1.62], 0.2693		0.72 [0.32, 1.61], 0.4189	
RD [95%-CI]; p-value	0.00 [-0.20, 0.20], 1.0000		-0.12 [-0.34, 0.10], 0.2870		-0.06 [-0.21, 0.09], 0.4310	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3193		0.1824		0.0755	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	11/43 (25.6)	8/26 (30.8)	13/53 (24.5)	3/20 (15.0)	24/96 (25.0)	11/46 (23.9)
RR [95%-CI]; p-value	0.83 [0.39, 1.79], 0.6382		1.64 [0.52, 5.14], 0.4000		1.05 [0.56, 1.95], 0.8884	
OR [95%-CI]; p-value	0.77 [0.26, 2.27], 0.6402		1.84 [0.46, 7.30], 0.3801		1.06 [0.47, 2.41], 0.8881	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.17], 0.6442		0.10 [-0.10, 0.29], 0.3375		0.01 [-0.14, 0.16], 0.8875	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	7/22 (31.8)	4/44 (9.1)	7/28 (25.0)	9/94 (9.6)	14/50 (28.0)
RR [95%-CI]; p-value	0.31 [0.11, 0.88], 0.0280		0.36 [0.12, 1.13], 0.0802		0.34 [0.16, 0.73], 0.0059	
OR [95%-CI]; p-value	0.24 [0.07, 0.86], 0.0221		0.30 [0.08, 1.14], 0.0674		0.27 [0.11, 0.69], 0.0041	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0433		-0.16 [-0.34, 0.02], 0.0858		-0.18 [-0.32, -0.05], 0.0088	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	8/48 (16.7)	8/24 (33.3)	5/47 (10.6)	4/24 (16.7)	13/95 (13.7)	12/48 (25.0)
RR [95%-CI]; p-value	0.50 [0.21, 1.17], 0.1094		0.64 [0.19, 2.16], 0.4705		0.55 [0.27, 1.11], 0.0932	
OR [95%-CI]; p-value	0.40 [0.13, 1.25], 0.1088		0.60 [0.14, 2.46], 0.4702		0.48 [0.20, 1.14], 0.0925	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.05], 0.1306		-0.06 [-0.23, 0.11], 0.4951		-0.11 [-0.25, 0.03], 0.1148	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.6254		0.6749		0.5805	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	5/43 (11.6)	4/26 (15.4)	5/53 (9.4)	0/20 (0.0)	10/96 (10.4)	4/46 (8.7)
RR [95%-CI]; p-value	0.76 [0.22, 2.56], 0.6532		3.87 [0.22, 67.68], 0.3543		1.20 [0.40, 3.62], 0.7487	
OR [95%-CI]; p-value	0.72 [0.18, 2.98], 0.6534		4.17 [0.22, 79.89], 0.3067		1.22 [0.36, 4.12], 0.7475	
RD [95%-CI]; p-value	-0.04 [-0.21, 0.13], 0.6622		0.07 [-0.03, 0.17], 0.1841		0.02 [-0.08, 0.12], 0.7404	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	5/50 (10.0)	6/22 (27.3)	6/44 (13.6)	4/28 (14.3)	11/94 (11.7)	10/50 (20.0)
RR [95%-CI]; p-value	0.37 [0.13, 1.08], 0.0675		0.95 [0.30, 3.09], 0.9380		0.59 [0.27, 1.28], 0.1806	
OR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0606		0.95 [0.24, 3.71], 0.9381		0.53 [0.21, 1.35], 0.1792	
RD [95%-CI]; p-value	-0.17 [-0.38, 0.03], 0.0967		-0.01 [-0.17, 0.16], 0.9384		-0.08 [-0.21, 0.05], 0.2057	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	3/24 (12.5)	9/47 (19.1)	4/24 (16.7)	11/95 (11.6)	7/48 (14.6)
RR [95%-CI]; p-value	0.33 [0.06, 1.86], 0.2108		1.15 [0.39, 3.35], 0.7993		0.79 [0.33, 1.92], 0.6081	
OR [95%-CI]; p-value	0.30 [0.05, 1.96], 0.1898		1.18 [0.32, 4.33], 0.7981		0.77 [0.28, 2.12], 0.6090	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2563		0.02 [-0.16, 0.21], 0.7945		-0.03 [-0.15, 0.09], 0.6201	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.9523		0.9874		0.9506	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	5/96 (5.2)	3/46 (6.5)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		0.75 [0.07, 7.87], 0.8140		0.80 [0.20, 3.20], 0.7507	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		0.75 [0.06, 8.70], 0.8139		0.79 [0.18, 3.45], 0.7507	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		-0.01 [-0.12, 0.10], 0.8245		-0.01 [-0.10, 0.07], 0.7594	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	1/22 (4.5)	3/44 (6.8)	2/28 (7.1)	6/94 (6.4)	3/50 (6.0)
RR [95%-CI]; p-value	1.32 [0.15, 12.00], 0.8052		0.95 [0.17, 5.36], 0.9579		1.06 [0.28, 4.07], 0.9280	
OR [95%-CI]; p-value	1.34 [0.13, 13.65], 0.8040		0.95 [0.15, 6.08], 0.9579		1.07 [0.26, 4.47], 0.9280	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.7939		-0.00 [-0.12, 0.12], 0.9581		0.00 [-0.08, 0.09], 0.9273	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	2/24 (8.3)	7/47 (14.9)	4/24 (16.7)	12/95 (12.6)	6/48 (12.5)
RR [95%-CI]; p-value	1.25 [0.26, 5.98], 0.7799		0.89 [0.29, 2.75], 0.8447		1.01 [0.40, 2.53], 0.9821	
OR [95%-CI]; p-value	1.28 [0.23, 7.13], 0.7785		0.88 [0.23, 3.34], 0.8451		1.01 [0.35, 2.89], 0.9821	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7711		-0.02 [-0.20, 0.16], 0.8474		0.00 [-0.11, 0.12], 0.9821	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.0820		0.3690		0.2977	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	6/26 (23.1)	8/53 (15.1)	0/20 (0.0)	11/96 (11.5)	6/46 (13.0)
RR [95%-CI]; p-value	0.30 [0.08, 1.11], 0.0708		6.19 [0.37, 102.92], 0.2038		0.88 [0.35, 2.23], 0.7849	
OR [95%-CI]; p-value	0.25 [0.06, 1.11], 0.0543		7.11 [0.39, 129.92], 0.1281		0.86 [0.30, 2.50], 0.7854	
RD [95%-CI]; p-value	-0.16 [-0.34, 0.02], 0.0778		0.13 [0.01, 0.24], 0.0344		-0.02 [-0.13, 0.10], 0.7894	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	10/50 (20.0)	1/22 (4.5)	5/44 (11.4)	4/28 (14.3)	15/94 (16.0)	5/50 (10.0)
RR [95%-CI]; p-value	4.40 [0.60, 32.30], 0.1452		0.80 [0.23, 2.71], 0.7146		1.60 [0.62, 4.14], 0.3361	
OR [95%-CI]; p-value	5.25 [0.63, 43.84], 0.0931		0.77 [0.19, 3.15], 0.7147		1.71 [0.58, 5.01], 0.3250	
RD [95%-CI]; p-value	0.15 [0.01, 0.30], 0.0316		-0.03 [-0.19, 0.13], 0.7203		0.06 [-0.05, 0.17], 0.2943	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	5/24 (20.8)	4/47 (8.5)	3/24 (12.5)	9/95 (9.5)	8/48 (16.7)
RR [95%-CI]; p-value	0.50 [0.16, 1.56], 0.2328		0.68 [0.17, 2.80], 0.5941		0.57 [0.23, 1.38], 0.2119	
OR [95%-CI]; p-value	0.44 [0.11, 1.71], 0.2283		0.65 [0.13, 3.18], 0.5938		0.52 [0.19, 1.46], 0.2095	
RD [95%-CI]; p-value	-0.10 [-0.29, 0.08], 0.2673		-0.04 [-0.19, 0.11], 0.6128		-0.07 [-0.19, 0.05], 0.2430	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.6188		0.5596		0.3177	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	5/26 (19.2)	5/53 (9.4)	2/20 (10.0)	8/96 (8.3)	7/46 (15.2)
RR [95%-CI]; p-value	0.36 [0.09, 1.39], 0.1398		0.94 [0.20, 4.48], 0.9415		0.55 [0.21, 1.42], 0.2148	
OR [95%-CI]; p-value	0.32 [0.07, 1.45], 0.1234		0.94 [0.17, 5.27], 0.9416		0.51 [0.17, 1.49], 0.2117	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1566		-0.01 [-0.16, 0.15], 0.9423		-0.07 [-0.19, 0.05], 0.2513	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	1/22 (4.5)	5/44 (11.4)	1/28 (3.6)	8/94 (8.5)	2/50 (4.0)
RR [95%-CI]; p-value	1.32 [0.15, 12.00], 0.8052		3.18 [0.39, 25.83], 0.2787		2.13 [0.47, 9.64], 0.3274	
OR [95%-CI]; p-value	1.34 [0.13, 13.65], 0.8040		3.46 [0.38, 31.32], 0.2435		2.23 [0.46, 10.94], 0.3107	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.7939		0.08 [-0.04, 0.19], 0.1890		0.05 [-0.03, 0.12], 0.2589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	3/24 (12.5)	5/47 (10.6)	3/24 (12.5)	8/95 (8.4)	6/48 (12.5)
RR [95%-CI]; p-value	0.50 [0.11, 2.29], 0.3725		0.85 [0.22, 3.26], 0.8141		0.67 [0.25, 1.83], 0.4388	
OR [95%-CI]; p-value	0.47 [0.09, 2.51], 0.3657		0.83 [0.18, 3.83], 0.8145		0.64 [0.21, 1.97], 0.4383	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4109		-0.02 [-0.18, 0.14], 0.8185		-0.04 [-0.15, 0.07], 0.4631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.2.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.4917		0.1687		0.4286	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	4/43 (9.3)	4/26 (15.4)	2/53 (3.8)	1/20 (5.0)	6/96 (6.3)	5/46 (10.9)
RR [95%-CI]; p-value	0.60 [0.17, 2.21], 0.4473		0.75 [0.07, 7.87], 0.8140		0.58 [0.19, 1.79], 0.3387	
OR [95%-CI]; p-value	0.56 [0.13, 2.48], 0.4444		0.75 [0.06, 8.70], 0.8139		0.55 [0.16, 1.89], 0.3352	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.10], 0.4663		-0.01 [-0.12, 0.10], 0.8245		-0.05 [-0.15, 0.06], 0.3754	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	4/22 (18.2)	5/44 (11.4)	0/28 (0.0)	11/94 (11.7)	4/50 (8.0)
RR [95%-CI]; p-value	0.66 [0.21, 2.11], 0.4832		6.48 [0.37, 114.08], 0.2018		1.46 [0.49, 4.36], 0.4947	
OR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4847		7.18 [0.38, 136.81], 0.1312		1.52 [0.46, 5.06], 0.4887	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5117		0.10 [-0.01, 0.20], 0.0741		0.04 [-0.06, 0.14], 0.4653	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	1/24 (4.2)	4/47 (8.5)	6/24 (25.0)	9/95 (9.5)	7/48 (14.6)
RR [95%-CI]; p-value	2.50 [0.31, 20.22], 0.3903		0.34 [0.11, 1.09], 0.0700		0.65 [0.26, 1.64], 0.3606	
OR [95%-CI]; p-value	2.67 [0.29, 24.28], 0.3657		0.28 [0.07, 1.11], 0.0588		0.61 [0.21, 1.76], 0.3600	
RD [95%-CI]; p-value	0.06 [-0.06, 0.18], 0.2981		-0.16 [-0.36, 0.03], 0.0902		-0.05 [-0.17, 0.06], 0.3876	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_2_m_soc_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.4.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8658		0.9155		0.6005	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	6/26 (23.1)	2/53 (3.8)	0/20 (0.0)	4/96 (4.2)	6/46 (13.0)
RR [95%-CI]; p-value	0.20 [0.04, 0.93], 0.0395		1.55 [0.07, 32.89], 0.7796		0.32 [0.09, 1.08], 0.0657	
OR [95%-CI]; p-value	0.16 [0.03, 0.88], 0.0205		1.57 [0.07, 36.31], 0.7771		0.29 [0.08, 1.08], 0.0530	
RD [95%-CI]; p-value	-0.18 [-0.36, -0.01], 0.0377		0.01 [-0.07, 0.10], 0.7561		-0.09 [-0.19, 0.02], 0.0982	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	1/50 (2.0)	1/22 (4.5)	1/44 (2.3)	0/28 (0.0)	2/94 (2.1)	1/50 (2.0)
RR [95%-CI]; p-value	0.44 [0.03, 6.72], 0.5550		1.30 [0.04, 37.37], 0.8800		1.06 [0.10, 11.45], 0.9593	
OR [95%-CI]; p-value	0.43 [0.03, 7.18], 0.5449		1.30 [0.04, 40.13], 0.8796		1.07 [0.09, 12.04], 0.9593	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.6006		0.01 [-0.06, 0.07], 0.8763		0.00 [-0.05, 0.05], 0.9589	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	6/95 (6.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.30 [0.08, 1.15], 0.0793		3.13 [0.16, 59.98], 0.4493		0.61 [0.19, 1.89], 0.3875	
OR [95%-CI]; p-value	0.25 [0.05, 1.17], 0.0634		3.27 [0.16, 68.07], 0.4193		0.58 [0.17, 2.01], 0.3848	
RD [95%-CI]; p-value	-0.15 [-0.32, 0.03], 0.1050		0.04 [-0.05, 0.13], 0.3419		-0.04 [-0.14, 0.06], 0.4183	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_4_m_pt_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.4.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.4268		0.4688		0.4917	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	3/43 (7.0)	2/26 (7.7)	2/53 (3.8)	0/20 (0.0)	5/96 (5.2)	2/46 (4.3)
RR [95%-CI]; p-value	0.91 [0.16, 5.07], 0.9115		1.55 [0.07, 32.89], 0.7796		1.20 [0.24, 5.94], 0.8251	
OR [95%-CI]; p-value	0.90 [0.14, 5.78], 0.9115		1.57 [0.07, 36.31], 0.7771		1.21 [0.23, 6.48], 0.8246	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.12], 0.9125		0.01 [-0.07, 0.10], 0.7561		0.01 [-0.07, 0.08], 0.8193	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	3/22 (13.6)	2/44 (4.5)	3/28 (10.7)	4/94 (4.3)	6/50 (12.0)
RR [95%-CI]; p-value	0.29 [0.05, 1.63], 0.1616		0.42 [0.08, 2.38], 0.3300		0.35 [0.10, 1.20], 0.0952	
OR [95%-CI]; p-value	0.26 [0.04, 1.71], 0.1384		0.40 [0.06, 2.54], 0.3155		0.33 [0.09, 1.21], 0.0818	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.06], 0.2181		-0.06 [-0.19, 0.07], 0.3525		-0.08 [-0.18, 0.02], 0.1248	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	5/24 (20.8)	3/47 (6.4)	0/24 (0.0)	5/95 (5.3)	5/48 (10.4)
RR [95%-CI]; p-value	0.20 [0.04, 0.96], 0.0438		3.13 [0.16, 59.98], 0.4493		0.51 [0.15, 1.66], 0.2609	
OR [95%-CI]; p-value	0.17 [0.03, 0.93], 0.0244		3.27 [0.16, 68.07], 0.4193		0.48 [0.13, 1.74], 0.2538	
RD [95%-CI]; p-value	-0.17 [-0.34, 0.01], 0.0576		0.04 [-0.05, 0.13], 0.3419		-0.05 [-0.15, 0.05], 0.2997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_4_m_pt_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.4.s6
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.4190		0.3717		0.1901	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	2/43 (4.7)	3/26 (11.5)	1/53 (1.9)	1/20 (5.0)	3/96 (3.1)	4/46 (8.7)
RR [95%-CI]; p-value	0.40 [0.07, 2.25], 0.3010		0.38 [0.02, 5.75], 0.4831		0.36 [0.08, 1.54], 0.1681	
OR [95%-CI]; p-value	0.37 [0.06, 2.40], 0.2849		0.37 [0.02, 6.14], 0.4674		0.34 [0.07, 1.58], 0.1513	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3280		-0.03 [-0.13, 0.07], 0.5509		-0.06 [-0.14, 0.03], 0.2176	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	4/50 (8.0)	1/22 (4.5)	3/44 (6.8)	0/28 (0.0)	7/94 (7.4)	1/50 (2.0)
RR [95%-CI]; p-value	1.76 [0.21, 14.86], 0.6035		3.89 [0.20, 74.74], 0.3682		3.72 [0.47, 29.42], 0.2126	
OR [95%-CI]; p-value	1.83 [0.19, 17.35], 0.5953		4.10 [0.20, 85.00], 0.3259		3.94 [0.47, 32.99], 0.1743	
RD [95%-CI]; p-value	0.03 [-0.08, 0.15], 0.5561		0.05 [-0.04, 0.14], 0.2632		0.05 [-0.01, 0.12], 0.1044	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	1/24 (4.2)	4/47 (8.5)	5/24 (20.8)	8/95 (8.4)	6/48 (12.5)
RR [95%-CI]; p-value	2.00 [0.24, 16.93], 0.5247		0.41 [0.12, 1.38], 0.1502		0.67 [0.25, 1.83], 0.4388	
OR [95%-CI]; p-value	2.09 [0.22, 19.81], 0.5121		0.35 [0.09, 1.46], 0.1399		0.64 [0.21, 1.97], 0.4383	
RD [95%-CI]; p-value	0.04 [-0.07, 0.15], 0.4652		-0.12 [-0.30, 0.06], 0.1821		-0.04 [-0.15, 0.07], 0.4631	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_4_m_pt_ae1pct_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.1368		0.8007		0.2227	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	1/43 (2.3)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	3/96 (3.1)	3/46 (6.5)
RR [95%-CI]; p-value	0.30 [0.03, 3.17], 0.3185		0.75 [0.07, 7.87], 0.8140		0.48 [0.10, 2.28], 0.3557	
OR [95%-CI]; p-value	0.29 [0.02, 3.32], 0.2895		0.75 [0.06, 8.70], 0.8139		0.46 [0.09, 2.39], 0.3464	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3472		-0.01 [-0.12, 0.10], 0.8245		-0.03 [-0.11, 0.05], 0.4017	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	0/22 (0.0)	1/44 (2.3)	2/28 (7.1)	3/94 (3.2)	2/50 (4.0)
RR [95%-CI]; p-value	1.80 [0.08, 38.34], 0.7064		0.32 [0.03, 3.35], 0.3402		0.80 [0.14, 4.62], 0.8010	
OR [95%-CI]; p-value	1.83 [0.08, 42.35], 0.7011		0.30 [0.03, 3.50], 0.3134		0.79 [0.13, 4.90], 0.8008	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6694		-0.05 [-0.15, 0.06], 0.3636		-0.01 [-0.07, 0.06], 0.8071	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	12/48 (25.0)	0/24 (0.0)	6/47 (12.8)	4/24 (16.7)	18/95 (18.9)	4/48 (8.3)
RR [95%-CI]; p-value	12.25 [0.75, 198.80], 0.0780		0.77 [0.24, 2.46], 0.6539		2.27 [0.81, 6.35], 0.1167	
OR [95%-CI]; p-value	16.00 [0.90, 283.81], 0.0144		0.73 [0.19, 2.89], 0.6549		2.57 [0.82, 8.08], 0.0967	
RD [95%-CI]; p-value	0.23 [0.09, 0.36], 0.0008		-0.04 [-0.22, 0.14], 0.6658		0.11 [-0.00, 0.22], 0.0609	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8042		0.8719		0.5343	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	0/26 (0.0)	0/53 (0.0)	0/20 (0.0)	0/96 (0.0)	0/46 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	0/44 (0.0)	1/28 (3.6)	0/94 (0.0)	1/50 (2.0)
RR [95%-CI]; p-value	NA		0.31 [0.01, 9.07], 0.5002		0.26 [0.01, 7.75], 0.4403	
OR [95%-CI]; p-value	NA		0.31 [0.01, 9.46], 0.4759		0.26 [0.01, 7.91], 0.4066	
RD [95%-CI]; p-value	NA		-0.02 [-0.10, 0.05], 0.5245		-0.01 [-0.06, 0.03], 0.4869	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	0/24 (0.0)	1/47 (2.1)	0/24 (0.0)	3/95 (3.2)	0/48 (0.0)
RR [95%-CI]; p-value	2.04 [0.10, 43.57], 0.6476		1.04 [0.04, 30.00], 0.9806		3.06 [0.16, 59.94], 0.4606	
OR [95%-CI]; p-value	2.09 [0.09, 48.12], 0.6389		1.04 [0.03, 32.23], 0.9806		3.13 [0.15, 63.77], 0.4346	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6005		0.00 [-0.07, 0.07], 0.9805		0.02 [-0.02, 0.07], 0.3566	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.1657		0.9920		0.3503	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	1/43 (2.3)	2/26 (7.7)	2/53 (3.8)	1/20 (5.0)	3/96 (3.1)	3/46 (6.5)
RR [95%-CI]; p-value	0.30 [0.03, 3.17], 0.3185		0.75 [0.07, 7.87], 0.8140		0.48 [0.10, 2.28], 0.3557	
OR [95%-CI]; p-value	0.29 [0.02, 3.32], 0.2895		0.75 [0.06, 8.70], 0.8139		0.46 [0.09, 2.39], 0.3464	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.06], 0.3472		-0.01 [-0.12, 0.10], 0.8245		-0.03 [-0.11, 0.05], 0.4017	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	0/22 (0.0)	1/44 (2.3)	1/28 (3.6)	3/94 (3.2)	1/50 (2.0)
RR [95%-CI]; p-value	1.80 [0.08, 38.34], 0.7064		0.64 [0.04, 9.77], 0.7457		1.60 [0.17, 14.94], 0.6822	
OR [95%-CI]; p-value	1.83 [0.08, 42.35], 0.7011		0.63 [0.04, 10.46], 0.7437		1.62 [0.16, 15.95], 0.6787	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6694		-0.01 [-0.09, 0.07], 0.7552		0.01 [-0.04, 0.06], 0.6572	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	10/48 (20.8)	0/24 (0.0)	5/47 (10.6)	4/24 (16.7)	15/95 (15.8)	4/48 (8.3)
RR [95%-CI]; p-value	10.21 [0.62, 167.58], 0.1037		0.64 [0.19, 2.16], 0.4705		1.89 [0.67, 5.40], 0.2315	
OR [95%-CI]; p-value	12.63 [0.70, 226.35], 0.0315		0.60 [0.14, 2.46], 0.4702		2.06 [0.64, 6.60], 0.2148	
RD [95%-CI]; p-value	0.19 [0.06, 0.32], 0.0040		-0.06 [-0.23, 0.11], 0.4951		0.07 [-0.03, 0.18], 0.1728	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.6393		0.7957		0.4225	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	1/43 (2.3)	1/26 (3.8)	0/53 (0.0)	0/20 (0.0)	1/96 (1.0)	1/46 (2.2)
RR [95%-CI]; p-value	0.60 [0.04, 9.26], 0.7178		NA		0.48 [0.03, 7.49], 0.6000	
OR [95%-CI]; p-value	0.60 [0.04, 9.94], 0.7152		NA		0.47 [0.03, 7.75], 0.5921	
RD [95%-CI]; p-value	-0.02 [-0.10, 0.07], 0.7306		NA		-0.01 [-0.06, 0.04], 0.6352	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	2/50 (4.0)	0/22 (0.0)	1/44 (2.3)	0/28 (0.0)	3/94 (3.2)	0/50 (0.0)
RR [95%-CI]; p-value	1.80 [0.08, 38.34], 0.7064		1.30 [0.04, 37.37], 0.8800		3.22 [0.16, 63.10], 0.4405	
OR [95%-CI]; p-value	1.83 [0.08, 42.35], 0.7011		1.30 [0.04, 40.13], 0.8796		3.30 [0.16, 67.13], 0.4118	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6694		0.01 [-0.06, 0.07], 0.8763		0.02 [-0.02, 0.07], 0.3357	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	4/48 (8.3)	0/24 (0.0)	2/47 (4.3)	0/24 (0.0)	6/95 (6.3)	0/48 (0.0)
RR [95%-CI]; p-value	4.08 [0.22, 74.17], 0.3416		2.09 [0.10, 44.48], 0.6379		6.13 [0.35, 107.42], 0.2148	
OR [95%-CI]; p-value	4.36 [0.22, 86.06], 0.2936		2.13 [0.09, 49.21], 0.6285		6.47 [0.35, 118.36], 0.1499	
RD [95%-CI]; p-value	0.06 [-0.03, 0.16], 0.1997		0.02 [-0.06, 0.10], 0.5893		0.05 [-0.00, 0.11], 0.0671	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.1910		0.3152		0.0481	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	4/26 (15.4)	3/53 (5.7)	2/20 (10.0)	3/96 (3.1)	6/46 (13.0)
RR [95%-CI]; p-value	0.07 [0.00, 1.36], 0.0795		0.57 [0.10, 3.14], 0.5151		0.24 [0.06, 0.92], 0.0367	
OR [95%-CI]; p-value	0.06 [0.00, 1.26], 0.0196		0.54 [0.08, 3.50], 0.5127		0.22 [0.05, 0.90], 0.0232	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0498		-0.04 [-0.19, 0.10], 0.5587		-0.10 [-0.20, 0.00], 0.0600	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	7/50 (14.0)	2/22 (9.1)	6/44 (13.6)	1/28 (3.6)	13/94 (13.8)	3/50 (6.0)
RR [95%-CI]; p-value	1.54 [0.35, 6.83], 0.5699		3.82 [0.49, 30.06], 0.2031		2.30 [0.69, 7.71], 0.1753	
OR [95%-CI]; p-value	1.63 [0.31, 8.55], 0.5618		4.26 [0.48, 37.48], 0.1599		2.51 [0.68, 9.28], 0.1546	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5318		0.10 [-0.02, 0.22], 0.1073		0.08 [-0.02, 0.17], 0.1097	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	5/48 (10.4)	3/24 (12.5)	4/47 (8.5)	3/24 (12.5)	9/95 (9.5)	6/48 (12.5)
RR [95%-CI]; p-value	0.83 [0.22, 3.20], 0.7905		0.68 [0.17, 2.80], 0.5941		0.76 [0.29, 2.01], 0.5765	
OR [95%-CI]; p-value	0.81 [0.18, 3.73], 0.7909		0.65 [0.13, 3.18], 0.5938		0.73 [0.24, 2.19], 0.5770	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.14], 0.7961		-0.04 [-0.19, 0.11], 0.6128		-0.03 [-0.14, 0.08], 0.5916	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8042		0.7315		0.9433	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	0/26 (0.0)	1/53 (1.9)	0/20 (0.0)	1/96 (1.0)	0/46 (0.0)
RR [95%-CI]; p-value	NA		0.77 [0.03, 22.19], 0.8808		0.97 [0.03, 28.36], 0.9853	
OR [95%-CI]; p-value	NA		0.77 [0.02, 23.84], 0.8806		0.97 [0.03, 29.40], 0.9853	
RD [95%-CI]; p-value	NA		-0.01 [-0.08, 0.07], 0.8870		-0.00 [-0.04, 0.04], 0.9854	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	0/50 (0.0)	0/22 (0.0)	2/44 (4.5)	0/28 (0.0)	2/94 (2.1)	0/50 (0.0)
RR [95%-CI]; p-value	NA		2.59 [0.12, 55.42], 0.5424		2.15 [0.10, 46.76], 0.6264	
OR [95%-CI]; p-value	NA		2.67 [0.12, 61.34], 0.5247		2.17 [0.10, 49.14], 0.6170	
RD [95%-CI]; p-value	NA		0.03 [-0.05, 0.11], 0.4841		0.01 [-0.03, 0.05], 0.5769	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	0/24 (0.0)	1/47 (2.1)	1/24 (4.2)	3/95 (3.2)	1/48 (2.1)
RR [95%-CI]; p-value	2.04 [0.10, 43.57], 0.6476		0.51 [0.03, 7.81], 0.6292		1.52 [0.16, 14.19], 0.7155	
OR [95%-CI]; p-value	2.09 [0.09, 48.12], 0.6389		0.50 [0.03, 8.36], 0.6233		1.53 [0.16, 15.14], 0.7129	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6005		-0.02 [-0.11, 0.07], 0.6569		0.01 [-0.04, 0.06], 0.6942	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.1704		0.2756		0.0309	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	4/26 (15.4)	2/53 (3.8)	2/20 (10.0)	2/96 (2.1)	6/46 (13.0)
RR [95%-CI]; p-value	0.07 [0.00, 1.36], 0.0795		0.38 [0.06, 2.50], 0.3125		0.16 [0.03, 0.76], 0.0213	
OR [95%-CI]; p-value	0.06 [0.00, 1.26], 0.0196		0.35 [0.05, 2.69], 0.2972		0.14 [0.03, 0.73], 0.0080	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0498		-0.06 [-0.20, 0.08], 0.3872		-0.11 [-0.21, -0.01], 0.0342	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	7/50 (14.0)	2/22 (9.1)	5/44 (11.4)	1/28 (3.6)	12/94 (12.8)	3/50 (6.0)
RR [95%-CI]; p-value	1.54 [0.35, 6.83], 0.5699		3.18 [0.39, 25.83], 0.2787		2.13 [0.63, 7.19], 0.2243	
OR [95%-CI]; p-value	1.63 [0.31, 8.55], 0.5618		3.46 [0.38, 31.32], 0.2435		2.29 [0.62, 8.54], 0.2057	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5318		0.08 [-0.04, 0.19], 0.1890		0.07 [-0.03, 0.16], 0.1595	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	3/48 (6.3)	3/24 (12.5)	3/47 (6.4)	3/24 (12.5)	6/95 (6.3)	6/48 (12.5)
RR [95%-CI]; p-value	0.50 [0.11, 2.29], 0.3725		0.51 [0.11, 2.34], 0.3870		0.51 [0.17, 1.48], 0.2141	
OR [95%-CI]; p-value	0.47 [0.09, 2.51], 0.3657		0.48 [0.09, 2.57], 0.3807		0.47 [0.14, 1.55], 0.2078	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4109		-0.06 [-0.21, 0.09], 0.4230		-0.06 [-0.17, 0.04], 0.2509	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.7.s6
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8290		0.4836		0.6201	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	0/43 (0.0)	0/26 (0.0)	2/53 (3.8)	0/20 (0.0)	2/96 (2.1)	0/46 (0.0)
RR [95%-CI]; p-value	NA		1.55 [0.07, 32.89], 0.7796		1.94 [0.09, 42.12], 0.6738	
OR [95%-CI]; p-value	NA		1.57 [0.07, 36.31], 0.7771		1.96 [0.09, 44.28], 0.6674	
RD [95%-CI]; p-value	NA		0.01 [-0.07, 0.10], 0.7561		0.01 [-0.03, 0.05], 0.6313	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	3/50 (6.0)	0/22 (0.0)	3/44 (6.8)	0/28 (0.0)	6/94 (6.4)	0/50 (0.0)
RR [95%-CI]; p-value	2.70 [0.14, 51.70], 0.5096		3.89 [0.20, 74.74], 0.3682		6.45 [0.37, 113.10], 0.2023	
OR [95%-CI]; p-value	2.81 [0.13, 58.50], 0.4875		4.10 [0.20, 85.00], 0.3259		6.82 [0.37, 124.63], 0.1359	
RD [95%-CI]; p-value	0.04 [-0.05, 0.13], 0.4090		0.05 [-0.04, 0.14], 0.2632		0.05 [-0.00, 0.11], 0.0612	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	2/48 (4.2)	0/24 (0.0)	0/47 (0.0)	1/24 (4.2)	2/95 (2.1)	1/48 (2.1)
RR [95%-CI]; p-value	2.04 [0.10, 43.57], 0.6476		0.25 [0.01, 7.27], 0.4221		1.01 [0.09, 10.87], 0.9931	
OR [95%-CI]; p-value	2.09 [0.09, 48.12], 0.6389		0.24 [0.01, 7.56], 0.3856		1.01 [0.09, 11.43], 0.9931	
RD [95%-CI]; p-value	0.02 [-0.06, 0.10], 0.6005		-0.03 [-0.12, 0.05], 0.4730		0.00 [-0.05, 0.05], 0.9931	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema. In AE severity analysis, a subject is only counted once with the maximum severity.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_7_m_pt_smq_ttlpth.sas using SAS 9.4

Table 12.4.4.1.6.s6
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.9131		0.6583		0.7402	
1st Tertile:	N1=43	N1=26	N1=53	N1=20	N1=96	N1=46
n/N1 (%)	7/43 (16.3)	7/26 (26.9)	10/53 (18.9)	2/20 (10.0)	17/96 (17.7)	9/46 (19.6)
RR [95%-CI]; p-value	0.60 [0.24, 1.53], 0.2878		1.89 [0.45, 7.87], 0.3837		0.91 [0.44, 1.87], 0.7882	
OR [95%-CI]; p-value	0.53 [0.16, 1.73], 0.2867		2.09 [0.42, 10.52], 0.3619		0.88 [0.36, 2.17], 0.7889	
RD [95%-CI]; p-value	-0.11 [-0.31, 0.10], 0.3043		0.09 [-0.08, 0.26], 0.3022		-0.02 [-0.16, 0.12], 0.7916	
2nd Tertile:	N2=50	N2=22	N2=44	N2=28	N2=94	N2=50
n/N2 (%)	6/50 (12.0)	4/22 (18.2)	4/44 (9.1)	3/28 (10.7)	10/94 (10.6)	7/50 (14.0)
RR [95%-CI]; p-value	0.66 [0.21, 2.11], 0.4832		0.85 [0.21, 3.51], 0.8206		0.76 [0.31, 1.87], 0.5511	
OR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4847		0.83 [0.17, 4.04], 0.8207		0.73 [0.26, 2.06], 0.5517	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5117		-0.02 [-0.16, 0.13], 0.8235		-0.03 [-0.15, 0.08], 0.5654	
3rd Tertile:	N3=48	N3=24	N3=47	N3=24	N3=95	N3=48
n/N3 (%)	11/48 (22.9)	7/24 (29.2)	14/47 (29.8)	4/24 (16.7)	25/95 (26.3)	11/48 (22.9)
RR [95%-CI]; p-value	0.79 [0.35, 1.77], 0.5601		1.79 [0.66, 4.84], 0.2534		1.15 [0.62, 2.13], 0.6611	
OR [95%-CI]; p-value	0.72 [0.24, 2.19], 0.5637		2.12 [0.61, 7.35], 0.2293		1.20 [0.53, 2.71], 0.6583	
RD [95%-CI]; p-value	-0.06 [-0.28, 0.15], 0.5729		0.13 [-0.07, 0.33], 0.1947		0.03 [-0.11, 0.18], 0.6532	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth/T12_4_4_1_6_m_pt_adr_ttlpth.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.3360		0.0648		0.0083	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	12/18 (66.7)	5/5 (100.0)	16/32 (50.0)	4/5 (80.0)	28/50 (56.0)	9/10 (90.0)
RR [95%-CI]; p-value	0.73 [0.48, 1.12], 0.1480		0.63 [0.36, 1.09], 0.0992		0.62 [0.45, 0.86], 0.0038	
OR [95%-CI]; p-value	0.20 [0.01, 4.30], 0.2660		0.25 [0.03, 2.49], 0.2106		0.14 [0.02, 1.20], 0.0435	
RD [95%-CI]; p-value	-0.24 [-0.57, 0.08], 0.1428		-0.30 [-0.69, 0.09], 0.1327		-0.34 [-0.57, -0.11], 0.0040	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	80/108 (74.1)	51/63 (81.0)	66/98 (67.3)	37/61 (60.7)	146/206 (70.9)	88/124 (71.0)
RR [95%-CI]; p-value	0.92 [0.78, 1.08], 0.2877		1.11 [0.87, 1.42], 0.4018		1.00 [0.87, 1.15], 0.9855	
OR [95%-CI]; p-value	0.67 [0.31, 1.44], 0.3054		1.34 [0.69, 2.60], 0.3904		1.00 [0.61, 1.63], 0.9855	
RD [95%-CI]; p-value	-0.07 [-0.20, 0.06], 0.2900		0.07 [-0.09, 0.22], 0.3938		-0.00 [-0.10, 0.10], 0.9855	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.8769		0.4316		0.8433	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	0/5 (0.0)	3/32 (9.4)	0/5 (0.0)	4/50 (8.0)	0/10 (0.0)
RR [95%-CI]; p-value	0.61 [0.02, 15.88], 0.7670		1.03 [0.06, 17.90], 0.9831		1.68 [0.10, 29.44], 0.7225	
OR [95%-CI]; p-value	0.59 [0.02, 20.24], 0.7666		1.03 [0.04, 23.92], 0.9831		1.74 [0.09, 35.58], 0.7162	
RD [95%-CI]; p-value	-0.04 [-0.30, 0.23], 0.7918		0.00 [-0.26, 0.26], 0.9830		0.03 [-0.12, 0.18], 0.6705	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	15/108 (13.9)	11/63 (17.5)	12/98 (12.2)	2/61 (3.3)	27/206 (13.1)	13/124 (10.5)
RR [95%-CI]; p-value	0.80 [0.39, 1.62], 0.5295		3.73 [0.87, 16.12], 0.0774		1.25 [0.67, 2.33], 0.4824	
OR [95%-CI]; p-value	0.76 [0.33, 1.78], 0.5304		4.12 [0.89, 19.07], 0.0524		1.29 [0.64, 2.60], 0.4795	
RD [95%-CI]; p-value	-0.04 [-0.15, 0.08], 0.5399		0.09 [0.01, 0.17], 0.0257		0.03 [-0.04, 0.10], 0.4686	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.0304		0.8160		0.0842	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	2/50 (4.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.34 [0.01, 9.06], 0.5224		0.20 [0.03, 1.26], 0.0862	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.32 [0.01, 10.94], 0.5095		0.17 [0.02, 1.36], 0.0641	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.06 [-0.31, 0.19], 0.6369		-0.16 [-0.41, 0.09], 0.2166	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	4/63 (6.3)	5/98 (5.1)	6/61 (9.8)	19/206 (9.2)	10/124 (8.1)
RR [95%-CI]; p-value	2.04 [0.70, 5.93], 0.1898		0.52 [0.17, 1.63], 0.2603		1.14 [0.55, 2.38], 0.7195	
OR [95%-CI]; p-value	2.20 [0.69, 6.99], 0.1740		0.49 [0.14, 1.69], 0.2527		1.16 [0.52, 2.58], 0.7188	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1380		-0.05 [-0.13, 0.04], 0.2834		0.01 [-0.05, 0.07], 0.7146	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.1782		0.8680		0.2373	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	5/32 (15.6)	1/5 (20.0)	8/50 (16.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.78 [0.11, 5.38], 0.8020		0.53 [0.17, 1.67], 0.2798	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.74 [0.07, 8.08], 0.8050		0.44 [0.09, 2.09], 0.2963	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.04 [-0.42, 0.33], 0.8179		-0.14 [-0.44, 0.16], 0.3630	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	22/108 (20.4)	10/63 (15.9)	12/98 (12.2)	8/61 (13.1)	34/206 (16.5)	18/124 (14.5)
RR [95%-CI]; p-value	1.28 [0.65, 2.53], 0.4720		0.93 [0.40, 2.15], 0.8721		1.14 [0.67, 1.92], 0.6324	
OR [95%-CI]; p-value	1.36 [0.60, 3.08], 0.4670		0.92 [0.35, 2.41], 0.8722		1.16 [0.63, 2.16], 0.6311	
RD [95%-CI]; p-value	0.04 [-0.07, 0.16], 0.4549		-0.01 [-0.12, 0.10], 0.8731		0.02 [-0.06, 0.10], 0.6265	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.7106		0.0720		0.3556	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	0/5 (0.0)	2/32 (6.3)	1/5 (20.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.61 [0.02, 15.88], 0.7670		0.31 [0.03, 2.84], 0.3018		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	0.59 [0.02, 20.24], 0.7666		0.27 [0.02, 3.65], 0.2949		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	-0.04 [-0.30, 0.23], 0.7918		-0.14 [-0.50, 0.22], 0.4547		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	10/108 (9.3)	5/63 (7.9)	8/98 (8.2)	1/61 (1.6)	18/206 (8.7)	6/124 (4.8)
RR [95%-CI]; p-value	1.17 [0.42, 3.26], 0.7687		4.98 [0.64, 38.84], 0.1256		1.81 [0.74, 4.43], 0.1964	
OR [95%-CI]; p-value	1.18 [0.39, 3.63], 0.7680		5.33 [0.65, 43.74], 0.0834		1.88 [0.73, 4.88], 0.1865	
RD [95%-CI]; p-value	0.01 [-0.07, 0.10], 0.7638		0.07 [0.00, 0.13], 0.0420		0.04 [-0.01, 0.09], 0.1568	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8493		0.2491		0.5048	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	0/5 (0.0)	1/32 (3.1)	1/5 (20.0)	2/50 (4.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.61 [0.02, 15.88], 0.7670		0.16 [0.01, 2.12], 0.1628		0.40 [0.04, 4.00], 0.4354	
OR [95%-CI]; p-value	0.59 [0.02, 20.24], 0.7666		0.13 [0.01, 2.49], 0.1207		0.38 [0.03, 4.59], 0.4268	
RD [95%-CI]; p-value	-0.04 [-0.30, 0.23], 0.7918		-0.17 [-0.52, 0.19], 0.3525		-0.06 [-0.25, 0.13], 0.5438	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	3/108 (2.8)	2/63 (3.2)	2/98 (2.0)	1/61 (1.6)	5/206 (2.4)	3/124 (2.4)
RR [95%-CI]; p-value	0.88 [0.15, 5.10], 0.8819		1.24 [0.12, 13.44], 0.8568		1.00 [0.24, 4.13], 0.9964	
OR [95%-CI]; p-value	0.87 [0.14, 5.36], 0.8819		1.25 [0.11, 14.09], 0.8564		1.00 [0.24, 4.27], 0.9964	
RD [95%-CI]; p-value	-0.00 [-0.06, 0.05], 0.8839		0.00 [-0.04, 0.05], 0.8528		0.00 [-0.03, 0.03], 0.9964	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.5065		0.5895		0.3603	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	2/50 (4.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		0.34 [0.01, 9.06], 0.5224		0.40 [0.04, 4.00], 0.4354	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		0.32 [0.01, 10.94], 0.5095		0.38 [0.03, 4.59], 0.4268	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		-0.06 [-0.31, 0.19], 0.6369		-0.06 [-0.25, 0.13], 0.5438	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	1/108 (0.9)	0/63 (0.0)	1/98 (1.0)	0/61 (0.0)	2/206 (1.0)	0/124 (0.0)
RR [95%-CI]; p-value	1.18 [0.04, 34.56], 0.9251		1.26 [0.04, 36.85], 0.8952		2.42 [0.11, 53.18], 0.5757	
OR [95%-CI]; p-value	1.18 [0.04, 35.60], 0.9250		1.26 [0.04, 38.06], 0.8949		2.43 [0.11, 54.35], 0.5627	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9235		0.00 [-0.03, 0.03], 0.8922		0.01 [-0.01, 0.02], 0.5213	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.2188		0.0084		0.0008	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	10/18 (55.6)	5/5 (100.0)	11/32 (34.4)	4/5 (80.0)	21/50 (42.0)	9/10 (90.0)
RR [95%-CI]; p-value	0.61 [0.37, 1.00], 0.0491		0.43 [0.22, 0.82], 0.0107		0.47 [0.32, 0.69], 0.0001	
OR [95%-CI]; p-value	0.13 [0.01, 2.65], 0.1310		0.13 [0.01, 1.32], 0.0533		0.08 [0.01, 0.68], 0.0056	
RD [95%-CI]; p-value	-0.35 [-0.69, -0.02], 0.0370		-0.46 [-0.84, -0.07], 0.0210		-0.48 [-0.71, -0.25], <0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	66/108 (61.1)	45/63 (71.4)	53/98 (54.1)	29/61 (47.5)	119/206 (57.8)	74/124 (59.7)
RR [95%-CI]; p-value	0.86 [0.69, 1.06], 0.1585		1.14 [0.83, 1.57], 0.4306		0.97 [0.80, 1.17], 0.7316	
OR [95%-CI]; p-value	0.63 [0.32, 1.23], 0.1727		1.30 [0.68, 2.47], 0.4223		0.92 [0.59, 1.45], 0.7330	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.04], 0.1619		0.07 [-0.09, 0.22], 0.4216		-0.02 [-0.13, 0.09], 0.7325	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.7955		0.3719		0.6748	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	7/18 (38.9)	2/5 (40.0)	10/32 (31.3)	2/5 (40.0)	17/50 (34.0)	4/10 (40.0)
RR [95%-CI]; p-value	0.97 [0.29, 3.29], 0.9639		0.78 [0.24, 2.57], 0.6844		0.85 [0.36, 1.99], 0.7084	
OR [95%-CI]; p-value	0.95 [0.13, 7.23], 0.9641		0.68 [0.10, 4.74], 0.6975		0.77 [0.19, 3.11], 0.7165	
RD [95%-CI]; p-value	-0.01 [-0.50, 0.47], 0.9642		-0.09 [-0.55, 0.37], 0.7083		-0.06 [-0.39, 0.27], 0.7222	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	38/108 (35.2)	27/63 (42.9)	34/98 (34.7)	15/61 (24.6)	72/206 (35.0)	42/124 (33.9)
RR [95%-CI]; p-value	0.82 [0.56, 1.20], 0.3130		1.41 [0.84, 2.37], 0.1916		1.03 [0.76, 1.40], 0.8419	
OR [95%-CI]; p-value	0.72 [0.38, 1.37], 0.3188		1.63 [0.80, 3.33], 0.1797		1.05 [0.66, 1.68], 0.8415	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.08], 0.3219		0.10 [-0.04, 0.24], 0.1672		0.01 [-0.09, 0.12], 0.8412	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.3.1.s7
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.0304		0.8160		0.0842	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	2/50 (4.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.34 [0.01, 9.06], 0.5224		0.20 [0.03, 1.26], 0.0862	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.32 [0.01, 10.94], 0.5095		0.17 [0.02, 1.36], 0.0641	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.06 [-0.31, 0.19], 0.6369		-0.16 [-0.41, 0.09], 0.2166	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	4/63 (6.3)	5/98 (5.1)	6/61 (9.8)	19/206 (9.2)	10/124 (8.1)
RR [95%-CI]; p-value	2.04 [0.70, 5.93], 0.1898		0.52 [0.17, 1.63], 0.2603		1.14 [0.55, 2.38], 0.7195	
OR [95%-CI]; p-value	2.20 [0.69, 6.99], 0.1740		0.49 [0.14, 1.69], 0.2527		1.16 [0.52, 2.58], 0.7188	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1380		-0.05 [-0.13, 0.04], 0.2834		0.01 [-0.05, 0.07], 0.7146	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_3_1_m_sf_ttl_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1647		0.8309		0.3196	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		1.03 [0.06, 17.90], 0.9831		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		1.03 [0.04, 23.92], 0.9831		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		0.00 [-0.26, 0.26], 0.9830		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	7/63 (11.1)	7/98 (7.1)	3/61 (4.9)	16/206 (7.8)	10/124 (8.1)
RR [95%-CI]; p-value	0.75 [0.29, 1.92], 0.5476		1.45 [0.39, 5.41], 0.5778		0.96 [0.45, 2.06], 0.9226	
OR [95%-CI]; p-value	0.73 [0.26, 2.06], 0.5474		1.49 [0.37, 5.98], 0.5742		0.96 [0.42, 2.19], 0.9226	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.5603		0.02 [-0.05, 0.10], 0.5581		-0.00 [-0.06, 0.06], 0.9229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6605		0.4194		0.9695	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	1/5 (20.0)	6/32 (18.8)	1/5 (20.0)	10/50 (20.0)	2/10 (20.0)
RR [95%-CI]; p-value	1.11 [0.16, 7.84], 0.9159		0.94 [0.14, 6.24], 0.9468		1.00 [0.26, 3.89], 1.0000	
OR [95%-CI]; p-value	1.14 [0.10, 13.34], 0.9151		0.92 [0.09, 9.82], 0.9471		1.00 [0.18, 5.46], 1.0000	
RD [95%-CI]; p-value	0.02 [-0.38, 0.42], 0.9132		-0.01 [-0.39, 0.36], 0.9480		0.00 [-0.27, 0.27], 1.0000	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	19/63 (30.2)	18/98 (18.4)	5/61 (8.2)	41/206 (19.9)	24/124 (19.4)
RR [95%-CI]; p-value	0.71 [0.42, 1.19], 0.1916		2.24 [0.88, 5.72], 0.0918		1.03 [0.65, 1.62], 0.9036	
OR [95%-CI]; p-value	0.63 [0.31, 1.27], 0.1940		2.52 [0.88, 7.19], 0.0762		1.04 [0.59, 1.82], 0.9035	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2053		0.10 [-0.00, 0.20], 0.0530		0.01 [-0.08, 0.09], 0.9032	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1588		0.1185		0.0384	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	2/5 (40.0)	4/50 (8.0)	4/10 (40.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.23 [0.05, 1.07], 0.0615		0.20 [0.06, 0.67], 0.0090	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.16 [0.02, 1.33], 0.0625		0.13 [0.03, 0.66], 0.0066	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.31 [-0.75, 0.13], 0.1736		-0.32 [-0.63, -0.01], 0.0450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	16/108 (14.8)	13/63 (20.6)	12/98 (12.2)	8/61 (13.1)	28/206 (13.6)	21/124 (16.9)
RR [95%-CI]; p-value	0.72 [0.37, 1.39], 0.3270		0.93 [0.40, 2.15], 0.8721		0.80 [0.48, 1.35], 0.4073	
OR [95%-CI]; p-value	0.67 [0.30, 1.50], 0.3279		0.92 [0.35, 2.41], 0.8722		0.77 [0.42, 1.43], 0.4081	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3431		-0.01 [-0.12, 0.10], 0.8731		-0.03 [-0.11, 0.05], 0.4181	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.6716		0.7312		0.4767	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	5/18 (27.8)	2/5 (40.0)	5/32 (15.6)	1/5 (20.0)	10/50 (20.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.69 [0.19, 2.57], 0.5844		0.78 [0.11, 5.38], 0.8020		0.67 [0.22, 2.00], 0.4688	
OR [95%-CI]; p-value	0.58 [0.07, 4.55], 0.5993		0.74 [0.07, 8.08], 0.8050		0.58 [0.13, 2.67], 0.4835	
RD [95%-CI]; p-value	-0.12 [-0.60, 0.35], 0.6153		-0.04 [-0.42, 0.33], 0.8179		-0.10 [-0.40, 0.20], 0.5203	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	29/108 (26.9)	18/63 (28.6)	25/98 (25.5)	14/61 (23.0)	54/206 (26.2)	32/124 (25.8)
RR [95%-CI]; p-value	0.94 [0.57, 1.55], 0.8075		1.11 [0.63, 1.97], 0.7166		1.02 [0.70, 1.48], 0.9350	
OR [95%-CI]; p-value	0.92 [0.46, 1.83], 0.8080		1.15 [0.54, 2.43], 0.7153		1.02 [0.61, 1.70], 0.9350	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.8089		0.03 [-0.11, 0.16], 0.7129		0.00 [-0.09, 0.10], 0.9349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8605		0.4487		0.8944	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	0/5 (0.0)	2/32 (6.3)	0/5 (0.0)	5/50 (10.0)	0/10 (0.0)
RR [95%-CI]; p-value	1.83 [0.11, 31.30], 0.6755		0.69 [0.04, 13.32], 0.8043		2.10 [0.12, 35.58], 0.6074	
OR [95%-CI]; p-value	2.00 [0.08, 47.16], 0.6623		0.67 [0.03, 17.03], 0.8051		2.22 [0.11, 44.05], 0.5914	
RD [95%-CI]; p-value	0.08 [-0.22, 0.37], 0.6154		-0.03 [-0.28, 0.23], 0.8268		0.05 [-0.10, 0.21], 0.5031	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	5/63 (7.9)	8/98 (8.2)	2/61 (3.3)	20/206 (9.7)	7/124 (5.6)
RR [95%-CI]; p-value	1.40 [0.52, 3.79], 0.5079		2.49 [0.55, 11.34], 0.2383		1.72 [0.75, 3.95], 0.2012	
OR [95%-CI]; p-value	1.45 [0.49, 4.33], 0.5033		2.62 [0.54, 12.78], 0.2173		1.80 [0.74, 4.38], 0.1921	
RD [95%-CI]; p-value	0.03 [-0.06, 0.12], 0.4858		0.05 [-0.02, 0.12], 0.1730		0.04 [-0.02, 0.10], 0.1646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5811		0.6751		0.9787	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	8/50 (16.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.56 [0.14, 2.20], 0.4032		1.38 [0.08, 22.55], 0.8234		0.80 [0.20, 3.22], 0.7535	
OR [95%-CI]; p-value	0.43 [0.05, 3.52], 0.4232		1.43 [0.06, 31.40], 0.8202		0.76 [0.14, 4.27], 0.7567	
RD [95%-CI]; p-value	-0.18 [-0.65, 0.29], 0.4589		0.03 [-0.23, 0.30], 0.8018		-0.04 [-0.31, 0.23], 0.7698	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	8/63 (12.7)	7/98 (7.1)	6/61 (9.8)	19/206 (9.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.88 [0.38, 2.02], 0.7551		0.73 [0.26, 2.06], 0.5475		0.82 [0.43, 1.57], 0.5441	
OR [95%-CI]; p-value	0.86 [0.33, 2.23], 0.7554		0.71 [0.23, 2.21], 0.5467		0.80 [0.38, 1.66], 0.5444	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.09], 0.7589		-0.03 [-0.12, 0.06], 0.5596		-0.02 [-0.09, 0.05], 0.5530	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0133		0.0628		0.0004	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	5/5 (100.0)	3/32 (9.4)	2/5 (40.0)	6/50 (12.0)	7/10 (70.0)
RR [95%-CI]; p-value	0.18 [0.06, 0.53], 0.0018		0.23 [0.05, 1.07], 0.0615		0.17 [0.07, 0.40], <0.0001	
OR [95%-CI]; p-value	0.02 [0.00, 0.47], 0.0013		0.16 [0.02, 1.33], 0.0625		0.06 [0.01, 0.29], <0.0001	
RD [95%-CI]; p-value	-0.74 [-1.00, -0.45], <0.0001		-0.31 [-0.75, 0.13], 0.1736		-0.58 [-0.88, -0.28], 0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	16/63 (25.4)	20/98 (20.4)	11/61 (18.0)	43/206 (20.9)	27/124 (21.8)
RR [95%-CI]; p-value	0.84 [0.48, 1.46], 0.5357		1.13 [0.58, 2.20], 0.7144		0.96 [0.63, 1.47], 0.8462	
OR [95%-CI]; p-value	0.79 [0.38, 1.65], 0.5376		1.17 [0.51, 2.64], 0.7131		0.95 [0.55, 1.63], 0.8463	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5437		0.02 [-0.10, 0.15], 0.7100		-0.01 [-0.10, 0.08], 0.8469	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4783		0.6825		0.9674	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	6/50 (12.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.28 [0.05, 1.51], 0.1376		1.38 [0.08, 22.55], 0.8234		0.60 [0.14, 2.56], 0.4896	
OR [95%-CI]; p-value	0.19 [0.02, 1.90], 0.1316		1.43 [0.06, 31.40], 0.8202		0.55 [0.09, 3.20], 0.4969	
RD [95%-CI]; p-value	-0.29 [-0.74, 0.16], 0.2116		0.03 [-0.23, 0.30], 0.8018		-0.08 [-0.34, 0.18], 0.5522	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	19/108 (17.6)	21/63 (33.3)	17/98 (17.3)	14/61 (23.0)	36/206 (17.5)	35/124 (28.2)
RR [95%-CI]; p-value	0.53 [0.31, 0.90], 0.0197		0.76 [0.40, 1.42], 0.3846		0.62 [0.41, 0.93], 0.0214	
OR [95%-CI]; p-value	0.43 [0.21, 0.88], 0.0190		0.70 [0.32, 1.56], 0.3858		0.54 [0.32, 0.92], 0.0214	
RD [95%-CI]; p-value	-0.16 [-0.29, -0.02], 0.0241		-0.06 [-0.19, 0.07], 0.3962		-0.11 [-0.20, -0.01], 0.0261	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.3894		0.1248		0.0753	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	1/5 (20.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.01, 3.48], 0.2271		0.16 [0.01, 2.12], 0.1628		0.10 [0.01, 1.00], 0.0500	
OR [95%-CI]; p-value	0.11 [0.00, 3.92], 0.1604		0.13 [0.01, 2.49], 0.1207		0.08 [0.01, 1.01], 0.0171	
RD [95%-CI]; p-value	-0.17 [-0.53, 0.19], 0.3441		-0.17 [-0.52, 0.19], 0.3525		-0.18 [-0.43, 0.07], 0.1598	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	12/63 (19.0)	15/98 (15.3)	7/61 (11.5)	27/206 (13.1)	19/124 (15.3)
RR [95%-CI]; p-value	0.58 [0.28, 1.22], 0.1519		1.33 [0.58, 3.08], 0.5006		0.86 [0.50, 1.47], 0.5729	
OR [95%-CI]; p-value	0.53 [0.22, 1.27], 0.1495		1.39 [0.53, 3.64], 0.4963		0.83 [0.44, 1.57], 0.5735	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1711		0.04 [-0.07, 0.15], 0.4834		-0.02 [-0.10, 0.06], 0.5795	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4290		0.6515		0.3238	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	4/32 (12.5)	1/5 (20.0)	7/50 (14.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.63 [0.09, 4.52], 0.6415		0.47 [0.14, 1.50], 0.2016	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.57 [0.05, 6.48], 0.6482		0.38 [0.08, 1.83], 0.2152	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.08 [-0.44, 0.29], 0.6902		-0.16 [-0.46, 0.14], 0.2957	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	10/63 (15.9)	10/98 (10.2)	6/61 (9.8)	24/206 (11.7)	16/124 (12.9)
RR [95%-CI]; p-value	0.82 [0.39, 1.73], 0.5965		1.04 [0.40, 2.71], 0.9402		0.90 [0.50, 1.63], 0.7353	
OR [95%-CI]; p-value	0.79 [0.33, 1.90], 0.5972		1.04 [0.36, 3.03], 0.9402		0.89 [0.45, 1.75], 0.7356	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.6049		0.00 [-0.09, 0.10], 0.9400		-0.01 [-0.09, 0.06], 0.7383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7803		0.0999		0.2848	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.16 [0.01, 2.12], 0.1628		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	NA		0.13 [0.01, 2.49], 0.1207		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	NA		-0.17 [-0.52, 0.19], 0.3525		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	9/63 (14.3)	13/98 (13.3)	5/61 (8.2)	21/206 (10.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.52 [0.21, 1.28], 0.1528		1.62 [0.61, 4.31], 0.3359		0.90 [0.48, 1.71], 0.7539	
OR [95%-CI]; p-value	0.48 [0.18, 1.32], 0.1471		1.71 [0.58, 5.07], 0.3267		0.89 [0.44, 1.83], 0.7541	
RD [95%-CI]; p-value	-0.07 [-0.17, 0.03], 0.1756		0.05 [-0.05, 0.15], 0.3016		-0.01 [-0.08, 0.06], 0.7567	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.1.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9729		0.0420		0.1170	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	2/5 (40.0)	4/50 (8.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.08 [0.01, 0.71], 0.0236		0.27 [0.07, 1.01], 0.0522	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.05 [0.00, 0.70], 0.0050		0.20 [0.04, 1.11], 0.0479	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.37 [-0.80, 0.06], 0.0956		-0.22 [-0.51, 0.07], 0.1422	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	11/108 (10.2)	8/63 (12.7)	8/98 (8.2)	5/61 (8.2)	19/206 (9.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.80 [0.34, 1.89], 0.6136		1.00 [0.34, 2.91], 0.9940		0.88 [0.45, 1.72], 0.7076	
OR [95%-CI]; p-value	0.78 [0.30, 2.05], 0.6139		1.00 [0.31, 3.20], 0.9940		0.87 [0.41, 1.82], 0.7078	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.6225		-0.00 [-0.09, 0.09], 0.9940		-0.01 [-0.08, 0.05], 0.7117	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_1_m_soc_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.3.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4408		0.1922		0.8676	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		0.34 [0.01, 9.06], 0.5224		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		0.32 [0.01, 10.94], 0.5095		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		-0.06 [-0.31, 0.19], 0.6369		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	11/63 (17.5)	5/98 (5.1)	0/61 (0.0)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.21 [0.07, 0.64], 0.0058		6.28 [0.35, 112.87], 0.2128		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.18 [0.06, 0.60], 0.0022		6.56 [0.35, 122.22], 0.1485		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.14 [-0.24, -0.04], 0.0072		0.04 [-0.01, 0.09], 0.0863		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_3_m_pt_ae10pct_dose.sas using SAS 9.4

Table 12.4.4.1.3.s7
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5216		0.4760		0.8182	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.34 [0.01, 9.06], 0.5224		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.32 [0.01, 10.94], 0.5095		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.06 [-0.31, 0.19], 0.6369		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	3/108 (2.8)	8/63 (12.7)	6/98 (6.1)	3/61 (4.9)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.22 [0.06, 0.79], 0.0209		1.24 [0.32, 4.80], 0.7502		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.20 [0.05, 0.77], 0.0107		1.26 [0.30, 5.24], 0.7493		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.10 [-0.19, -0.01], 0.0269		0.01 [-0.06, 0.08], 0.7433		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_3_m_pt_ae10pct_dose.sas using SAS 9.4

Table 12.4.8.1.1.s7
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.2864		0.4455		0.2523	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	0/32 (0.0)	0/5 (0.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		NA		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		NA		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		NA		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	5/108 (4.6)	2/63 (3.2)	4/98 (4.1)	3/61 (4.9)	9/206 (4.4)	5/124 (4.0)
RR [95%-CI]; p-value	1.46 [0.29, 7.30], 0.6460		0.83 [0.19, 3.58], 0.8027		1.08 [0.37, 3.16], 0.8832	
OR [95%-CI]; p-value	1.48 [0.28, 7.87], 0.6432		0.82 [0.18, 3.81], 0.8026		1.09 [0.36, 3.32], 0.8832	
RD [95%-CI]; p-value	0.01 [-0.04, 0.07], 0.6270		-0.01 [-0.08, 0.06], 0.8065		0.00 [-0.04, 0.05], 0.8820	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_8_1_1_m_soc_sae5pct_dose.sas using SAS 9.4

Table 12.4.8.1.2.s7
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_8_1_2_m_pt_sae5pct_dose.sas using SAS 9.4

Table 12.4.5.1.1.s7
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_5_1_1_m_soc_aeg35pct_dose.sas using SAS 9.4

Table 12.4.5.1.2.s7
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_5_1_2_m_pt_aeg35pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1647		0.8309		0.3196	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		1.03 [0.06, 17.90], 0.9831		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		1.03 [0.04, 23.92], 0.9831		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		0.00 [-0.26, 0.26], 0.9830		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	7/63 (11.1)	7/98 (7.1)	3/61 (4.9)	16/206 (7.8)	10/124 (8.1)
RR [95%-CI]; p-value	0.75 [0.29, 1.92], 0.5476		1.45 [0.39, 5.41], 0.5778		0.96 [0.45, 2.06], 0.9226	
OR [95%-CI]; p-value	0.73 [0.26, 2.06], 0.5474		1.49 [0.37, 5.98], 0.5742		0.96 [0.42, 2.19], 0.9226	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.5603		0.02 [-0.05, 0.10], 0.5581		-0.00 [-0.06, 0.06], 0.9229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6605		0.4194		0.9695	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	1/5 (20.0)	6/32 (18.8)	1/5 (20.0)	10/50 (20.0)	2/10 (20.0)
RR [95%-CI]; p-value	1.11 [0.16, 7.84], 0.9159		0.94 [0.14, 6.24], 0.9468		1.00 [0.26, 3.89], 1.0000	
OR [95%-CI]; p-value	1.14 [0.10, 13.34], 0.9151		0.92 [0.09, 9.82], 0.9471		1.00 [0.18, 5.46], 1.0000	
RD [95%-CI]; p-value	0.02 [-0.38, 0.42], 0.9132		-0.01 [-0.39, 0.36], 0.9480		0.00 [-0.27, 0.27], 1.0000	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	19/63 (30.2)	18/98 (18.4)	5/61 (8.2)	41/206 (19.9)	24/124 (19.4)
RR [95%-CI]; p-value	0.71 [0.42, 1.19], 0.1916		2.24 [0.88, 5.72], 0.0918		1.03 [0.65, 1.62], 0.9036	
OR [95%-CI]; p-value	0.63 [0.31, 1.27], 0.1940		2.52 [0.88, 7.19], 0.0762		1.04 [0.59, 1.82], 0.9035	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.2053		0.10 [-0.00, 0.20], 0.0530		0.01 [-0.08, 0.09], 0.9032	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1588		0.1185		0.0384	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	2/5 (40.0)	3/32 (9.4)	2/5 (40.0)	4/50 (8.0)	4/10 (40.0)
RR [95%-CI]; p-value	0.14 [0.02, 1.24], 0.0768		0.23 [0.05, 1.07], 0.0615		0.20 [0.06, 0.67], 0.0090	
OR [95%-CI]; p-value	0.09 [0.01, 1.31], 0.0431		0.16 [0.02, 1.33], 0.0625		0.13 [0.03, 0.66], 0.0066	
RD [95%-CI]; p-value	-0.34 [-0.79, 0.10], 0.1269		-0.31 [-0.75, 0.13], 0.1736		-0.32 [-0.63, -0.01], 0.0450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	16/108 (14.8)	13/63 (20.6)	12/98 (12.2)	8/61 (13.1)	28/206 (13.6)	21/124 (16.9)
RR [95%-CI]; p-value	0.72 [0.37, 1.39], 0.3270		0.93 [0.40, 2.15], 0.8721		0.80 [0.48, 1.35], 0.4073	
OR [95%-CI]; p-value	0.67 [0.30, 1.50], 0.3279		0.92 [0.35, 2.41], 0.8722		0.77 [0.42, 1.43], 0.4081	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3431		-0.01 [-0.12, 0.10], 0.8731		-0.03 [-0.11, 0.05], 0.4181	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.6716		0.7312		0.4767	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	5/18 (27.8)	2/5 (40.0)	5/32 (15.6)	1/5 (20.0)	10/50 (20.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.69 [0.19, 2.57], 0.5844		0.78 [0.11, 5.38], 0.8020		0.67 [0.22, 2.00], 0.4688	
OR [95%-CI]; p-value	0.58 [0.07, 4.55], 0.5993		0.74 [0.07, 8.08], 0.8050		0.58 [0.13, 2.67], 0.4835	
RD [95%-CI]; p-value	-0.12 [-0.60, 0.35], 0.6153		-0.04 [-0.42, 0.33], 0.8179		-0.10 [-0.40, 0.20], 0.5203	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	29/108 (26.9)	18/63 (28.6)	25/98 (25.5)	14/61 (23.0)	54/206 (26.2)	32/124 (25.8)
RR [95%-CI]; p-value	0.94 [0.57, 1.55], 0.8075		1.11 [0.63, 1.97], 0.7166		1.02 [0.70, 1.48], 0.9350	
OR [95%-CI]; p-value	0.92 [0.46, 1.83], 0.8080		1.15 [0.54, 2.43], 0.7153		1.02 [0.61, 1.70], 0.9350	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.12], 0.8089		0.03 [-0.11, 0.16], 0.7129		0.00 [-0.09, 0.10], 0.9349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8605		0.4487		0.8944	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	0/5 (0.0)	2/32 (6.3)	0/5 (0.0)	5/50 (10.0)	0/10 (0.0)
RR [95%-CI]; p-value	1.83 [0.11, 31.30], 0.6755		0.69 [0.04, 13.32], 0.8043		2.10 [0.12, 35.58], 0.6074	
OR [95%-CI]; p-value	2.00 [0.08, 47.16], 0.6623		0.67 [0.03, 17.03], 0.8051		2.22 [0.11, 44.05], 0.5914	
RD [95%-CI]; p-value	0.08 [-0.22, 0.37], 0.6154		-0.03 [-0.28, 0.23], 0.8268		0.05 [-0.10, 0.21], 0.5031	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	5/63 (7.9)	8/98 (8.2)	2/61 (3.3)	20/206 (9.7)	7/124 (5.6)
RR [95%-CI]; p-value	1.40 [0.52, 3.79], 0.5079		2.49 [0.55, 11.34], 0.2383		1.72 [0.75, 3.95], 0.2012	
OR [95%-CI]; p-value	1.45 [0.49, 4.33], 0.5033		2.62 [0.54, 12.78], 0.2173		1.80 [0.74, 4.38], 0.1921	
RD [95%-CI]; p-value	0.03 [-0.06, 0.12], 0.4858		0.05 [-0.02, 0.12], 0.1730		0.04 [-0.02, 0.10], 0.1646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5811		0.6751		0.9787	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	4/18 (22.2)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	8/50 (16.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.56 [0.14, 2.20], 0.4032		1.38 [0.08, 22.55], 0.8234		0.80 [0.20, 3.22], 0.7535	
OR [95%-CI]; p-value	0.43 [0.05, 3.52], 0.4232		1.43 [0.06, 31.40], 0.8202		0.76 [0.14, 4.27], 0.7567	
RD [95%-CI]; p-value	-0.18 [-0.65, 0.29], 0.4589		0.03 [-0.23, 0.30], 0.8018		-0.04 [-0.31, 0.23], 0.7698	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	8/63 (12.7)	7/98 (7.1)	6/61 (9.8)	19/206 (9.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.88 [0.38, 2.02], 0.7551		0.73 [0.26, 2.06], 0.5475		0.82 [0.43, 1.57], 0.5441	
OR [95%-CI]; p-value	0.86 [0.33, 2.23], 0.7554		0.71 [0.23, 2.21], 0.5467		0.80 [0.38, 1.66], 0.5444	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.09], 0.7589		-0.03 [-0.12, 0.06], 0.5596		-0.02 [-0.09, 0.05], 0.5530	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.0133		0.0628		0.0004	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	5/5 (100.0)	3/32 (9.4)	2/5 (40.0)	6/50 (12.0)	7/10 (70.0)
RR [95%-CI]; p-value	0.18 [0.06, 0.53], 0.0018		0.23 [0.05, 1.07], 0.0615		0.17 [0.07, 0.40], <0.0001	
OR [95%-CI]; p-value	0.02 [0.00, 0.47], 0.0013		0.16 [0.02, 1.33], 0.0625		0.06 [0.01, 0.29], <0.0001	
RD [95%-CI]; p-value	-0.74 [-1.00, -0.45], <0.0001		-0.31 [-0.75, 0.13], 0.1736		-0.58 [-0.88, -0.28], 0.0001	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	23/108 (21.3)	16/63 (25.4)	20/98 (20.4)	11/61 (18.0)	43/206 (20.9)	27/124 (21.8)
RR [95%-CI]; p-value	0.84 [0.48, 1.46], 0.5357		1.13 [0.58, 2.20], 0.7144		0.96 [0.63, 1.47], 0.8462	
OR [95%-CI]; p-value	0.79 [0.38, 1.65], 0.5376		1.17 [0.51, 2.64], 0.7131		0.95 [0.55, 1.63], 0.8463	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5437		0.02 [-0.10, 0.15], 0.7100		-0.01 [-0.10, 0.08], 0.8469	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4783		0.6825		0.9674	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	2/5 (40.0)	4/32 (12.5)	0/5 (0.0)	6/50 (12.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.28 [0.05, 1.51], 0.1376		1.38 [0.08, 22.55], 0.8234		0.60 [0.14, 2.56], 0.4896	
OR [95%-CI]; p-value	0.19 [0.02, 1.90], 0.1316		1.43 [0.06, 31.40], 0.8202		0.55 [0.09, 3.20], 0.4969	
RD [95%-CI]; p-value	-0.29 [-0.74, 0.16], 0.2116		0.03 [-0.23, 0.30], 0.8018		-0.08 [-0.34, 0.18], 0.5522	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	19/108 (17.6)	21/63 (33.3)	17/98 (17.3)	14/61 (23.0)	36/206 (17.5)	35/124 (28.2)
RR [95%-CI]; p-value	0.53 [0.31, 0.90], 0.0197		0.76 [0.40, 1.42], 0.3846		0.62 [0.41, 0.93], 0.0214	
OR [95%-CI]; p-value	0.43 [0.21, 0.88], 0.0190		0.70 [0.32, 1.56], 0.3858		0.54 [0.32, 0.92], 0.0214	
RD [95%-CI]; p-value	-0.16 [-0.29, -0.02], 0.0241		-0.06 [-0.19, 0.07], 0.3962		-0.11 [-0.20, -0.01], 0.0261	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.3894		0.1248		0.0753	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	1/5 (20.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.14 [0.01, 3.48], 0.2271		0.16 [0.01, 2.12], 0.1628		0.10 [0.01, 1.00], 0.0500	
OR [95%-CI]; p-value	0.11 [0.00, 3.92], 0.1604		0.13 [0.01, 2.49], 0.1207		0.08 [0.01, 1.01], 0.0171	
RD [95%-CI]; p-value	-0.17 [-0.53, 0.19], 0.3441		-0.17 [-0.52, 0.19], 0.3525		-0.18 [-0.43, 0.07], 0.1598	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	12/108 (11.1)	12/63 (19.0)	15/98 (15.3)	7/61 (11.5)	27/206 (13.1)	19/124 (15.3)
RR [95%-CI]; p-value	0.58 [0.28, 1.22], 0.1519		1.33 [0.58, 3.08], 0.5006		0.86 [0.50, 1.47], 0.5729	
OR [95%-CI]; p-value	0.53 [0.22, 1.27], 0.1495		1.39 [0.53, 3.64], 0.4963		0.83 [0.44, 1.57], 0.5735	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1711		0.04 [-0.07, 0.15], 0.4834		-0.02 [-0.10, 0.06], 0.5795	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.3214		0.1977		0.1002	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	1/32 (3.1)	1/5 (20.0)	2/50 (4.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		0.16 [0.01, 2.12], 0.1628		0.20 [0.03, 1.26], 0.0862	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		0.13 [0.01, 2.49], 0.1207		0.17 [0.02, 1.36], 0.0641	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		-0.17 [-0.52, 0.19], 0.3525		-0.16 [-0.41, 0.09], 0.2166	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	4/63 (6.3)	8/98 (8.2)	5/61 (8.2)	16/206 (7.8)	9/124 (7.3)
RR [95%-CI]; p-value	1.17 [0.37, 3.72], 0.7944		1.00 [0.34, 2.91], 0.9940		1.07 [0.49, 2.35], 0.8658	
OR [95%-CI]; p-value	1.18 [0.34, 4.09], 0.7939		1.00 [0.31, 3.20], 0.9940		1.08 [0.46, 2.51], 0.8656	
RD [95%-CI]; p-value	0.01 [-0.07, 0.09], 0.7900		-0.00 [-0.09, 0.09], 0.9940		0.01 [-0.05, 0.06], 0.8646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4290		0.6515		0.3238	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	4/32 (12.5)	1/5 (20.0)	7/50 (14.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.63 [0.09, 4.52], 0.6415		0.47 [0.14, 1.50], 0.2016	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.57 [0.05, 6.48], 0.6482		0.38 [0.08, 1.83], 0.2152	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.08 [-0.44, 0.29], 0.6902		-0.16 [-0.46, 0.14], 0.2957	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	14/108 (13.0)	10/63 (15.9)	10/98 (10.2)	6/61 (9.8)	24/206 (11.7)	16/124 (12.9)
RR [95%-CI]; p-value	0.82 [0.39, 1.73], 0.5965		1.04 [0.40, 2.71], 0.9402		0.90 [0.50, 1.63], 0.7353	
OR [95%-CI]; p-value	0.79 [0.33, 1.90], 0.5972		1.04 [0.36, 3.03], 0.9402		0.89 [0.45, 1.75], 0.7356	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.6049		0.00 [-0.09, 0.10], 0.9400		-0.01 [-0.09, 0.06], 0.7383	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.7803		0.0999		0.2848	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	1/32 (3.1)	1/5 (20.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.16 [0.01, 2.12], 0.1628		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	NA		0.13 [0.01, 2.49], 0.1207		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	NA		-0.17 [-0.52, 0.19], 0.3525		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	9/63 (14.3)	13/98 (13.3)	5/61 (8.2)	21/206 (10.2)	14/124 (11.3)
RR [95%-CI]; p-value	0.52 [0.21, 1.28], 0.1528		1.62 [0.61, 4.31], 0.3359		0.90 [0.48, 1.71], 0.7539	
OR [95%-CI]; p-value	0.48 [0.18, 1.32], 0.1471		1.71 [0.58, 5.07], 0.3267		0.89 [0.44, 1.83], 0.7541	
RD [95%-CI]; p-value	-0.07 [-0.17, 0.03], 0.1756		0.05 [-0.05, 0.15], 0.3016		-0.01 [-0.08, 0.06], 0.7567	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.2.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9729		0.0420		0.1170	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	2/5 (40.0)	4/50 (8.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.08 [0.01, 0.71], 0.0236		0.27 [0.07, 1.01], 0.0522	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.05 [0.00, 0.70], 0.0050		0.20 [0.04, 1.11], 0.0479	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.37 [-0.80, 0.06], 0.0956		-0.22 [-0.51, 0.07], 0.1422	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	11/108 (10.2)	8/63 (12.7)	8/98 (8.2)	5/61 (8.2)	19/206 (9.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.80 [0.34, 1.89], 0.6136		1.00 [0.34, 2.91], 0.9940		0.88 [0.45, 1.72], 0.7076	
OR [95%-CI]; p-value	0.78 [0.30, 2.05], 0.6139		1.00 [0.31, 3.20], 0.9940		0.87 [0.41, 1.82], 0.7078	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.6225		-0.00 [-0.09, 0.09], 0.9940		-0.01 [-0.08, 0.05], 0.7117	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_2_m_soc_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.4.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4408		0.1922		0.8676	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		0.34 [0.01, 9.06], 0.5224		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		0.32 [0.01, 10.94], 0.5095		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		-0.06 [-0.31, 0.19], 0.6369		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	11/63 (17.5)	5/98 (5.1)	0/61 (0.0)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.21 [0.07, 0.64], 0.0058		6.28 [0.35, 112.87], 0.2128		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.18 [0.06, 0.60], 0.0022		6.56 [0.35, 122.22], 0.1485		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.14 [-0.24, -0.04], 0.0072		0.04 [-0.01, 0.09], 0.0863		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_4_m_pt_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.4.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5216		0.4760		0.8182	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	2/5 (40.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.42 [0.09, 1.85], 0.2494		0.34 [0.01, 9.06], 0.5224		0.40 [0.08, 1.90], 0.2483	
OR [95%-CI]; p-value	0.30 [0.03, 2.65], 0.2631		0.32 [0.01, 10.94], 0.5095		0.35 [0.05, 2.23], 0.2482	
RD [95%-CI]; p-value	-0.23 [-0.70, 0.23], 0.3229		-0.06 [-0.31, 0.19], 0.6369		-0.12 [-0.38, 0.14], 0.3640	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	3/108 (2.8)	8/63 (12.7)	6/98 (6.1)	3/61 (4.9)	9/206 (4.4)	11/124 (8.9)
RR [95%-CI]; p-value	0.22 [0.06, 0.79], 0.0209		1.24 [0.32, 4.80], 0.7502		0.49 [0.21, 1.15], 0.1034	
OR [95%-CI]; p-value	0.20 [0.05, 0.77], 0.0107		1.26 [0.30, 5.24], 0.7493		0.47 [0.19, 1.17], 0.0969	
RD [95%-CI]; p-value	-0.10 [-0.19, -0.01], 0.0269		0.01 [-0.06, 0.08], 0.7433		-0.05 [-0.10, 0.01], 0.1236	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_4_m_pt_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.4.s7
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.6318		0.0772		0.0802	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	2/18 (11.1)	1/5 (20.0)	1/32 (3.1)	2/5 (40.0)	3/50 (6.0)	3/10 (30.0)
RR [95%-CI]; p-value	0.56 [0.06, 4.95], 0.5983		0.08 [0.01, 0.71], 0.0236		0.20 [0.05, 0.85], 0.0295	
OR [95%-CI]; p-value	0.50 [0.04, 7.00], 0.6016		0.05 [0.00, 0.70], 0.0050		0.15 [0.02, 0.89], 0.0209	
RD [95%-CI]; p-value	-0.09 [-0.47, 0.29], 0.6462		-0.37 [-0.80, 0.06], 0.0956		-0.24 [-0.53, 0.05], 0.1067	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	7/108 (6.5)	4/63 (6.3)	5/98 (5.1)	4/61 (6.6)	12/206 (5.8)	8/124 (6.5)
RR [95%-CI]; p-value	1.02 [0.31, 3.35], 0.9729		0.78 [0.22, 2.79], 0.6997		0.90 [0.38, 2.15], 0.8173	
OR [95%-CI]; p-value	1.02 [0.29, 3.64], 0.9729		0.77 [0.20, 2.97], 0.6994		0.90 [0.36, 2.26], 0.8173	
RD [95%-CI]; p-value	0.00 [-0.07, 0.08], 0.9728		-0.01 [-0.09, 0.06], 0.7070		-0.01 [-0.06, 0.05], 0.8194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_4_m_pt_ae1pct_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.2108		0.8160		0.7232	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.34 [0.01, 9.06], 0.5224		0.80 [0.10, 6.43], 0.8337	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.32 [0.01, 10.94], 0.5095		0.78 [0.08, 7.84], 0.8345	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.06 [-0.31, 0.19], 0.6369		-0.02 [-0.22, 0.18], 0.8450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	1/63 (1.6)	5/98 (5.1)	6/61 (9.8)	14/206 (6.8)	7/124 (5.6)
RR [95%-CI]; p-value	5.25 [0.68, 40.48], 0.1116		0.52 [0.17, 1.63], 0.2603		1.20 [0.50, 2.90], 0.6792	
OR [95%-CI]; p-value	5.64 [0.70, 45.58], 0.0698		0.49 [0.14, 1.69], 0.2527		1.22 [0.48, 3.11], 0.6783	
RD [95%-CI]; p-value	0.07 [0.01, 0.13], 0.0291		-0.05 [-0.13, 0.04], 0.2834		0.01 [-0.04, 0.06], 0.6716	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5963		0.8163		0.6609	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	0/32 (0.0)	0/5 (0.0)	0/50 (0.0)	0/10 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	1/108 (0.9)	0/63 (0.0)	0/98 (0.0)	1/61 (1.6)	1/206 (0.5)	1/124 (0.8)
RR [95%-CI]; p-value	1.18 [0.04, 34.56], 0.9251		0.31 [0.01, 9.09], 0.4966		0.60 [0.04, 9.54], 0.7188	
OR [95%-CI]; p-value	1.18 [0.04, 35.60], 0.9250		0.31 [0.01, 9.26], 0.4717		0.60 [0.04, 9.68], 0.7159	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9235		-0.01 [-0.05, 0.02], 0.5241		-0.00 [-0.02, 0.02], 0.7321	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2430		0.7384		0.6752	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	1/32 (3.1)	0/5 (0.0)	4/50 (8.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.34 [0.01, 9.06], 0.5224		0.80 [0.10, 6.43], 0.8337	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.32 [0.01, 10.94], 0.5095		0.78 [0.08, 7.84], 0.8345	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.06 [-0.31, 0.19], 0.6369		-0.02 [-0.22, 0.18], 0.8450	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	8/108 (7.4)	1/63 (1.6)	5/98 (5.1)	5/61 (8.2)	13/206 (6.3)	6/124 (4.8)
RR [95%-CI]; p-value	4.67 [0.60, 36.45], 0.1419		0.62 [0.19, 2.06], 0.4378		1.30 [0.51, 3.34], 0.5803	
OR [95%-CI]; p-value	4.96 [0.61, 40.62], 0.1002		0.60 [0.17, 2.17], 0.4344		1.32 [0.49, 3.58], 0.5782	
RD [95%-CI]; p-value	0.06 [-0.00, 0.12], 0.0502		-0.03 [-0.11, 0.05], 0.4565		0.01 [-0.04, 0.07], 0.5662	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.1556		0.4409		0.0910	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	1/18 (5.6)	1/5 (20.0)	0/32 (0.0)	0/5 (0.0)	1/50 (2.0)	1/10 (10.0)
RR [95%-CI]; p-value	0.28 [0.02, 3.70], 0.3321		NA		0.20 [0.01, 2.94], 0.2405	
OR [95%-CI]; p-value	0.24 [0.01, 4.62], 0.3106		NA		0.18 [0.01, 3.21], 0.1983	
RD [95%-CI]; p-value	-0.14 [-0.51, 0.22], 0.4395		NA		-0.08 [-0.27, 0.11], 0.4091	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	0/63 (0.0)	1/98 (1.0)	0/61 (0.0)	5/206 (2.4)	0/124 (0.0)
RR [95%-CI]; p-value	4.70 [0.25, 87.52], 0.2993		1.26 [0.04, 36.85], 0.8952		6.04 [0.33, 109.68], 0.2238	
OR [95%-CI]; p-value	4.85 [0.25, 93.20], 0.2486		1.26 [0.04, 38.06], 0.8949		6.17 [0.33, 113.89], 0.1631	
RD [95%-CI]; p-value	0.03 [-0.01, 0.07], 0.1707		0.00 [-0.03, 0.03], 0.8922		0.02 [-0.00, 0.04], 0.0949	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.6949		0.5243		0.8251	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	3/32 (9.4)	1/5 (20.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.47 [0.06, 3.67], 0.4705		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	NA		0.41 [0.03, 5.01], 0.4767		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	NA		-0.11 [-0.47, 0.26], 0.5682		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	10/108 (9.3)	9/63 (14.3)	8/98 (8.2)	5/61 (8.2)	18/206 (8.7)	14/124 (11.3)
RR [95%-CI]; p-value	0.65 [0.28, 1.51], 0.3146		1.00 [0.34, 2.91], 0.9940		0.77 [0.40, 1.50], 0.4480	
OR [95%-CI]; p-value	0.61 [0.23, 1.60], 0.3130		1.00 [0.31, 3.20], 0.9940		0.75 [0.36, 1.57], 0.4479	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3353		-0.00 [-0.09, 0.09], 0.9940		-0.03 [-0.09, 0.04], 0.4603	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.5963		0.2874		0.2791	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	0/32 (0.0)	0/5 (0.0)	0/50 (0.0)	0/10 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	1/108 (0.9)	0/63 (0.0)	3/98 (3.1)	1/61 (1.6)	4/206 (1.9)	1/124 (0.8)
RR [95%-CI]; p-value	1.18 [0.04, 34.56], 0.9251		1.87 [0.20, 17.55], 0.5848		2.41 [0.27, 21.30], 0.4295	
OR [95%-CI]; p-value	1.18 [0.04, 35.60], 0.9250		1.89 [0.19, 18.64], 0.5777		2.44 [0.27, 22.04], 0.4135	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9235		0.01 [-0.03, 0.06], 0.5505		0.01 [-0.01, 0.04], 0.3648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7349		0.6980		0.9502	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	3/32 (9.4)	1/5 (20.0)	3/50 (6.0)	1/10 (10.0)
RR [95%-CI]; p-value	NA		0.47 [0.06, 3.67], 0.4705		0.60 [0.07, 5.20], 0.6428	
OR [95%-CI]; p-value	NA		0.41 [0.03, 5.01], 0.4767		0.57 [0.05, 6.16], 0.6434	
RD [95%-CI]; p-value	NA		-0.11 [-0.47, 0.26], 0.5682		-0.04 [-0.24, 0.16], 0.6910	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	9/108 (8.3)	9/63 (14.3)	6/98 (6.1)	5/61 (8.2)	15/206 (7.3)	14/124 (11.3)
RR [95%-CI]; p-value	0.58 [0.24, 1.39], 0.2247		0.75 [0.24, 2.34], 0.6168		0.64 [0.32, 1.29], 0.2151	
OR [95%-CI]; p-value	0.55 [0.20, 1.46], 0.2212		0.73 [0.21, 2.51], 0.6162		0.62 [0.29, 1.33], 0.2129	
RD [95%-CI]; p-value	-0.06 [-0.16, 0.04], 0.2476		-0.02 [-0.10, 0.06], 0.6268		-0.04 [-0.11, 0.03], 0.2342	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.7.s7
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.2592		0.3228		0.2224	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	0/18 (0.0)	0/5 (0.0)	1/32 (3.1)	0/5 (0.0)	1/50 (2.0)	0/10 (0.0)
RR [95%-CI]; p-value	NA		0.34 [0.01, 9.06], 0.5224		0.42 [0.02, 11.72], 0.6095	
OR [95%-CI]; p-value	NA		0.32 [0.01, 10.94], 0.5095		0.41 [0.01, 13.02], 0.6008	
RD [95%-CI]; p-value	NA		-0.06 [-0.31, 0.19], 0.6369		-0.03 [-0.16, 0.11], 0.6874	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	4/108 (3.7)	0/63 (0.0)	4/98 (4.1)	1/61 (1.6)	8/206 (3.9)	1/124 (0.8)
RR [95%-CI]; p-value	4.70 [0.25, 87.52], 0.2993		2.49 [0.28, 21.76], 0.4095		4.82 [0.61, 38.04], 0.1361	
OR [95%-CI]; p-value	4.85 [0.25, 93.20], 0.2486		2.55 [0.28, 23.39], 0.3908		4.97 [0.61, 40.22], 0.0965	
RD [95%-CI]; p-value	0.03 [-0.01, 0.07], 0.1707		0.02 [-0.03, 0.07], 0.3432		0.03 [0.00, 0.06], 0.0496	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_7_m_pt_smq_dose.sas using SAS 9.4

Table 12.4.4.1.6.s7
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.7816		0.3367		0.6848	
1.Dose 30 ug	N1=18	N1=5	N1=32	N1=5	N1=50	N1=10
n/N1 (%)	3/18 (16.7)	1/5 (20.0)	4/32 (12.5)	1/5 (20.0)	7/50 (14.0)	2/10 (20.0)
RR [95%-CI]; p-value	0.83 [0.11, 6.38], 0.8606		0.63 [0.09, 4.52], 0.6415		0.70 [0.17, 2.89], 0.6218	
OR [95%-CI]; p-value	0.80 [0.06, 9.92], 0.8619		0.57 [0.05, 6.48], 0.6482		0.65 [0.11, 3.72], 0.6276	
RD [95%-CI]; p-value	-0.03 [-0.42, 0.36], 0.8672		-0.08 [-0.44, 0.29], 0.6902		-0.06 [-0.33, 0.21], 0.6583	
2.Dose 60 ug	N2=108	N2=63	N2=98	N2=61	N2=206	N2=124
n/N2 (%)	18/108 (16.7)	17/63 (27.0)	20/98 (20.4)	7/61 (11.5)	38/206 (18.4)	24/124 (19.4)
RR [95%-CI]; p-value	0.62 [0.34, 1.11], 0.1068		1.78 [0.80, 3.95], 0.1580		0.95 [0.60, 1.51], 0.8377	
OR [95%-CI]; p-value	0.54 [0.26, 1.15], 0.1067		1.98 [0.78, 5.00], 0.1446		0.94 [0.53, 1.66], 0.8379	
RD [95%-CI]; p-value	-0.10 [-0.23, 0.03], 0.1204		0.09 [-0.02, 0.20], 0.1212		-0.01 [-0.10, 0.08], 0.8386	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose/T12_4_4_1_6_m_pt_adr_dose.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.1886		0.2714		0.0491	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	17/23 (73.9)	11/11 (100.0)	13/21 (61.9)	7/9 (77.8)	30/44 (68.2)	18/20 (90.0)
RR [95%-CI]; p-value	0.77 [0.59, 1.01], 0.0635		0.80 [0.49, 1.29], 0.3556		0.76 [0.59, 0.97], 0.0290	
OR [95%-CI]; p-value	0.13 [0.01, 2.54], 0.1237		0.46 [0.08, 2.81], 0.3980		0.24 [0.05, 1.17], 0.0617	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.00], 0.0472		-0.16 [-0.50, 0.18], 0.3629		-0.22 [-0.41, -0.03], 0.0247	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	84/118 (71.2)	45/61 (73.8)	78/123 (63.4)	37/63 (58.7)	162/241 (67.2)	82/124 (66.1)
RR [95%-CI]; p-value	0.96 [0.80, 1.17], 0.7110		1.08 [0.84, 1.38], 0.5421		1.02 [0.87, 1.19], 0.8348	
OR [95%-CI]; p-value	0.88 [0.44, 1.76], 0.7149		1.22 [0.65, 2.27], 0.5337		1.05 [0.66, 1.66], 0.8339	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.7123		0.05 [-0.10, 0.20], 0.5361		0.01 [-0.09, 0.11], 0.8343	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.0442		0.2131		0.0164	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	4/11 (36.4)	3/21 (14.3)	1/9 (11.1)	4/44 (9.1)	5/20 (25.0)
RR [95%-CI]; p-value	0.12 [0.02, 0.95], 0.0443		1.29 [0.15, 10.76], 0.8166		0.36 [0.11, 1.21], 0.0996	
OR [95%-CI]; p-value	0.08 [0.01, 0.83], 0.0137		1.33 [0.12, 14.87], 0.8147		0.30 [0.07, 1.27], 0.0897	
RD [95%-CI]; p-value	-0.32 [-0.62, -0.02], 0.0342		0.03 [-0.22, 0.29], 0.8065		-0.16 [-0.37, 0.05], 0.1337	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	16/118 (13.6)	7/61 (11.5)	16/123 (13.0)	1/63 (1.6)	32/241 (13.3)	8/124 (6.5)
RR [95%-CI]; p-value	1.18 [0.51, 2.72], 0.6945		8.20 [1.11, 60.39], 0.0390		2.06 [0.98, 4.33], 0.0572	
OR [95%-CI]; p-value	1.21 [0.47, 3.12], 0.6929		9.27 [1.20, 71.61], 0.0105		2.22 [0.99, 4.98], 0.0480	
RD [95%-CI]; p-value	0.02 [-0.08, 0.12], 0.6861		0.11 [0.05, 0.18], 0.0008		0.07 [0.01, 0.13], 0.0279	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.4325		0.1586		0.8133	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	0/11 (0.0)	0/21 (0.0)	2/9 (22.2)	4/44 (9.1)	2/20 (10.0)
RR [95%-CI]; p-value	4.00 [0.23, 69.39], 0.3410		0.10 [0.01, 2.10], 0.1403		0.91 [0.18, 4.56], 0.9078	
OR [95%-CI]; p-value	4.63 [0.22, 96.08], 0.2835		0.08 [0.00, 2.07], 0.0677		0.90 [0.15, 5.37], 0.9079	
RD [95%-CI]; p-value	0.13 [-0.06, 0.33], 0.1891		-0.20 [-0.48, 0.08], 0.1622		-0.01 [-0.17, 0.15], 0.9094	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	6/61 (9.8)	10/123 (8.1)	5/63 (7.9)	24/241 (10.0)	11/124 (8.9)
RR [95%-CI]; p-value	1.21 [0.49, 2.98], 0.6847		1.02 [0.37, 2.87], 0.9634		1.12 [0.57, 2.22], 0.7389	
OR [95%-CI]; p-value	1.23 [0.45, 3.39], 0.6831		1.03 [0.34, 3.14], 0.9634		1.14 [0.54, 2.40], 0.7382	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6750		0.00 [-0.08, 0.08], 0.9633		0.01 [-0.05, 0.07], 0.7340	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.1584		0.1572		0.6028	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	9/23 (39.1)	1/11 (9.1)	1/21 (4.8)	2/9 (22.2)	10/44 (22.7)	3/20 (15.0)
RR [95%-CI]; p-value	4.30 [0.62, 29.86], 0.1397		0.21 [0.02, 2.07], 0.1835		1.52 [0.47, 4.92], 0.4890	
OR [95%-CI]; p-value	6.43 [0.70, 59.17], 0.0721		0.18 [0.01, 2.24], 0.1441		1.67 [0.40, 6.86], 0.4763	
RD [95%-CI]; p-value	0.30 [0.04, 0.56], 0.0246		-0.17 [-0.46, 0.11], 0.2323		0.08 [-0.12, 0.28], 0.4479	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	21/118 (17.8)	11/61 (18.0)	21/123 (17.1)	9/63 (14.3)	42/241 (17.4)	20/124 (16.1)
RR [95%-CI]; p-value	0.99 [0.51, 1.91], 0.9688		1.20 [0.58, 2.45], 0.6272		1.08 [0.66, 1.76], 0.7551	
OR [95%-CI]; p-value	0.98 [0.44, 2.20], 0.9688		1.24 [0.53, 2.88], 0.6247		1.10 [0.61, 1.97], 0.7544	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9689		0.03 [-0.08, 0.14], 0.6163		0.01 [-0.07, 0.09], 0.7520	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9368		0.6998		0.9320	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	7/23 (30.4)	2/11 (18.2)	1/21 (4.8)	0/9 (0.0)	8/44 (18.2)	2/20 (10.0)
RR [95%-CI]; p-value	1.67 [0.41, 6.77], 0.4700		0.90 [0.03, 24.71], 0.9527		1.82 [0.42, 7.80], 0.4211	
OR [95%-CI]; p-value	1.97 [0.34, 11.57], 0.4487		0.90 [0.03, 29.35], 0.9527		2.00 [0.38, 10.41], 0.4034	
RD [95%-CI]; p-value	0.12 [-0.17, 0.42], 0.4164		-0.01 [-0.17, 0.16], 0.9536		0.08 [-0.09, 0.26], 0.3567	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	9/118 (7.6)	3/61 (4.9)	14/123 (11.4)	4/63 (6.3)	23/241 (9.5)	7/124 (5.6)
RR [95%-CI]; p-value	1.55 [0.44, 5.52], 0.4981		1.79 [0.62, 5.22], 0.2845		1.69 [0.75, 3.83], 0.2083	
OR [95%-CI]; p-value	1.60 [0.42, 6.13], 0.4921		1.89 [0.60, 6.02], 0.2719		1.76 [0.73, 4.23], 0.1990	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.4632		0.05 [-0.03, 0.13], 0.2308		0.04 [-0.02, 0.09], 0.1648	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8835		0.6314		0.8399	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	2/44 (4.5)	0/20 (0.0)
RR [95%-CI]; p-value	2.00 [0.10, 40.86], 0.6525		0.44 [0.01, 20.66], 0.6771		1.86 [0.09, 39.52], 0.6895	
OR [95%-CI]; p-value	2.10 [0.09, 50.57], 0.6424		0.43 [0.01, 23.33], 0.6695		1.90 [0.08, 44.20], 0.6832	
RD [95%-CI]; p-value	0.04 [-0.12, 0.21], 0.6051		-0.03 [-0.19, 0.13], 0.7114		0.02 [-0.07, 0.11], 0.6494	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	2/61 (3.3)	7/123 (5.7)	3/63 (4.8)	13/241 (5.4)	5/124 (4.0)
RR [95%-CI]; p-value	1.55 [0.32, 7.46], 0.5839		1.20 [0.32, 4.46], 0.7910		1.34 [0.49, 3.67], 0.5717	
OR [95%-CI]; p-value	1.58 [0.31, 8.07], 0.5794		1.21 [0.30, 4.84], 0.7903		1.36 [0.47, 3.90], 0.5693	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5535		0.01 [-0.06, 0.08], 0.7847		0.01 [-0.03, 0.06], 0.5518	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.6123		0.5831		0.5722	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	0/23 (0.0)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	0/44 (0.0)	0/20 (0.0)
RR [95%-CI]; p-value	0.49 [0.01, 23.13], 0.7164		0.44 [0.01, 20.66], 0.6771		0.46 [0.01, 22.42], 0.6958	
OR [95%-CI]; p-value	0.48 [0.01, 25.73], 0.7112		0.43 [0.01, 23.33], 0.6695		0.45 [0.01, 23.73], 0.6889	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.11], 0.7407		-0.03 [-0.19, 0.13], 0.7114		-0.01 [-0.09, 0.06], 0.7261	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	3/118 (2.5)	1/61 (1.6)	3/123 (2.4)	1/63 (1.6)	6/241 (2.5)	2/124 (1.6)
RR [95%-CI]; p-value	1.55 [0.16, 14.60], 0.7013		1.54 [0.16, 14.47], 0.7074		1.54 [0.32, 7.54], 0.5915	
OR [95%-CI]; p-value	1.57 [0.16, 15.37], 0.6984		1.55 [0.16, 15.21], 0.7047		1.56 [0.31, 7.83], 0.5879	
RD [95%-CI]; p-value	0.01 [-0.03, 0.05], 0.6784		0.01 [-0.03, 0.05], 0.6852		0.01 [-0.02, 0.04], 0.5621	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.1348		0.6053		0.1567	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	11/23 (47.8)	9/11 (81.8)	12/21 (57.1)	6/9 (66.7)	23/44 (52.3)	15/20 (75.0)
RR [95%-CI]; p-value	0.58 [0.35, 0.97], 0.0390		0.86 [0.47, 1.55], 0.6099		0.70 [0.48, 1.02], 0.0620	
OR [95%-CI]; p-value	0.20 [0.04, 1.16], 0.0596		0.67 [0.13, 3.41], 0.6256		0.37 [0.11, 1.18], 0.0862	
RD [95%-CI]; p-value	-0.34 [-0.65, -0.03], 0.0295		-0.10 [-0.47, 0.28], 0.6174		-0.23 [-0.47, 0.01], 0.0639	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	71/118 (60.2)	41/61 (67.2)	58/123 (47.2)	29/63 (46.0)	129/241 (53.5)	70/124 (56.5)
RR [95%-CI]; p-value	0.90 [0.71, 1.13], 0.3426		1.02 [0.74, 1.42], 0.8849		0.95 [0.78, 1.15], 0.5915	
OR [95%-CI]; p-value	0.74 [0.38, 1.41], 0.3560		1.05 [0.57, 1.92], 0.8845		0.89 [0.57, 1.37], 0.5951	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3485		0.01 [-0.14, 0.16], 0.8845		-0.03 [-0.14, 0.08], 0.5943	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.4404		0.1185		0.5886	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	12/23 (52.2)	5/11 (45.5)	6/21 (28.6)	4/9 (44.4)	18/44 (40.9)	9/20 (45.0)
RR [95%-CI]; p-value	1.15 [0.54, 2.45], 0.7209		0.64 [0.24, 1.74], 0.3843		0.91 [0.50, 1.66], 0.7558	
OR [95%-CI]; p-value	1.31 [0.31, 5.53], 0.7139		0.50 [0.10, 2.53], 0.3980		0.85 [0.29, 2.46], 0.7587	
RD [95%-CI]; p-value	0.07 [-0.29, 0.43], 0.7131		-0.16 [-0.54, 0.22], 0.4102		-0.04 [-0.30, 0.22], 0.7596	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	38/118 (32.2)	24/61 (39.3)	43/123 (35.0)	14/63 (22.2)	81/241 (33.6)	38/124 (30.6)
RR [95%-CI]; p-value	0.82 [0.54, 1.23], 0.3348		1.57 [0.93, 2.65], 0.0883		1.10 [0.80, 1.51], 0.5701	
OR [95%-CI]; p-value	0.73 [0.39, 1.39], 0.3413		1.88 [0.93, 3.79], 0.0745		1.15 [0.72, 1.83], 0.5671	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3469		0.13 [-0.01, 0.26], 0.0602		0.03 [-0.07, 0.13], 0.5639	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.3.1.s8
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.4325		0.1586		0.8133	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	0/11 (0.0)	0/21 (0.0)	2/9 (22.2)	4/44 (9.1)	2/20 (10.0)
RR [95%-CI]; p-value	4.00 [0.23, 69.39], 0.3410		0.10 [0.01, 2.10], 0.1403		0.91 [0.18, 4.56], 0.9078	
OR [95%-CI]; p-value	4.63 [0.22, 96.08], 0.2835		0.08 [0.00, 2.07], 0.0677		0.90 [0.15, 5.37], 0.9079	
RD [95%-CI]; p-value	0.13 [-0.06, 0.33], 0.1891		-0.20 [-0.48, 0.08], 0.1622		-0.01 [-0.17, 0.15], 0.9094	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	6/61 (9.8)	10/123 (8.1)	5/63 (7.9)	24/241 (10.0)	11/124 (8.9)
RR [95%-CI]; p-value	1.21 [0.49, 2.98], 0.6847		1.02 [0.37, 2.87], 0.9634		1.12 [0.57, 2.22], 0.7389	
OR [95%-CI]; p-value	1.23 [0.45, 3.39], 0.6831		1.03 [0.34, 3.14], 0.9634		1.14 [0.54, 2.40], 0.7382	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6750		0.00 [-0.08, 0.08], 0.9633		0.01 [-0.05, 0.07], 0.7340	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_3_1_m_sf_ttl_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6827		0.8454		0.6000	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	1/21 (4.8)	0/9 (0.0)	4/44 (9.1)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.90 [0.03, 24.71], 0.9527		0.61 [0.15, 2.46], 0.4834	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.90 [0.03, 29.35], 0.9527		0.57 [0.11, 2.81], 0.4827	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.01 [-0.17, 0.16], 0.9536		-0.06 [-0.24, 0.12], 0.5154	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	6/61 (9.8)	10/123 (8.1)	4/63 (6.3)	18/241 (7.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.69 [0.25, 1.90], 0.4713		1.28 [0.42, 3.92], 0.6650		0.93 [0.44, 1.95], 0.8394	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4704		1.31 [0.39, 4.34], 0.6631		0.92 [0.41, 2.06], 0.8395	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.4932		0.02 [-0.06, 0.09], 0.6511		-0.01 [-0.06, 0.05], 0.8413	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8497		0.7577		0.8393	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	3/11 (27.3)	7/21 (33.3)	2/9 (22.2)	12/44 (27.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.80 [0.23, 2.75], 0.7196		1.50 [0.38, 5.87], 0.5601		1.09 [0.44, 2.68], 0.8496	
OR [95%-CI]; p-value	0.74 [0.14, 3.88], 0.7219		1.75 [0.29, 10.74], 0.5428		1.13 [0.34, 3.77], 0.8487	
RD [95%-CI]; p-value	-0.06 [-0.37, 0.26], 0.7286		0.11 [-0.23, 0.45], 0.5197		0.02 [-0.21, 0.25], 0.8470	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	23/118 (19.5)	17/61 (27.9)	19/123 (15.4)	5/63 (7.9)	42/241 (17.4)	22/124 (17.7)
RR [95%-CI]; p-value	0.70 [0.41, 1.21], 0.1989		1.95 [0.76, 4.97], 0.1637		0.98 [0.62, 1.57], 0.9403	
OR [95%-CI]; p-value	0.63 [0.30, 1.29], 0.2022		2.12 [0.75, 5.97], 0.1482		0.98 [0.55, 1.73], 0.9403	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2180		0.08 [-0.02, 0.17], 0.1111		-0.00 [-0.09, 0.08], 0.9405	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7284		0.0722		0.1454	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	0/21 (0.0)	3/9 (33.3)	2/44 (4.5)	4/20 (20.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.07 [0.00, 1.26], 0.0711		0.23 [0.05, 1.14], 0.0718	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.05 [0.00, 1.09], 0.0143		0.19 [0.03, 1.14], 0.0493	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.31 [-0.62, 0.00], 0.0533		-0.15 [-0.34, 0.03], 0.1030	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	17/118 (14.4)	14/61 (23.0)	17/123 (13.8)	8/63 (12.7)	34/241 (14.1)	22/124 (17.7)
RR [95%-CI]; p-value	0.63 [0.33, 1.19], 0.1515		1.09 [0.50, 2.38], 0.8322		0.80 [0.49, 1.30], 0.3598	
OR [95%-CI]; p-value	0.57 [0.26, 1.24], 0.1522		1.10 [0.45, 2.72], 0.8318		0.76 [0.42, 1.37], 0.3616	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1737		0.01 [-0.09, 0.11], 0.8298		-0.04 [-0.12, 0.04], 0.3752	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9811		0.4456		0.6764	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	8/23 (34.8)	4/11 (36.4)	5/21 (23.8)	1/9 (11.1)	13/44 (29.5)	5/20 (25.0)
RR [95%-CI]; p-value	0.96 [0.37, 2.50], 0.9278		2.14 [0.29, 15.83], 0.4551		1.18 [0.49, 2.87], 0.7116	
OR [95%-CI]; p-value	0.93 [0.21, 4.18], 0.9281		2.50 [0.25, 25.15], 0.4256		1.26 [0.38, 4.18], 0.7077	
RD [95%-CI]; p-value	-0.02 [-0.36, 0.33], 0.9283		0.13 [-0.15, 0.40], 0.3645		0.05 [-0.19, 0.28], 0.7019	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	30/118 (25.4)	16/61 (26.2)	28/123 (22.8)	15/63 (23.8)	58/241 (24.1)	31/124 (25.0)
RR [95%-CI]; p-value	0.97 [0.58, 1.63], 0.9068		0.96 [0.55, 1.66], 0.8726		0.96 [0.66, 1.41], 0.8437	
OR [95%-CI]; p-value	0.96 [0.47, 1.94], 0.9069		0.94 [0.46, 1.93], 0.8729		0.95 [0.58, 1.57], 0.8440	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.13], 0.9072		-0.01 [-0.14, 0.12], 0.8735		-0.01 [-0.10, 0.08], 0.8447	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8496		0.9217		0.7953	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	1/11 (9.1)	2/21 (9.5)	0/9 (0.0)	5/44 (11.4)	1/20 (5.0)
RR [95%-CI]; p-value	1.43 [0.17, 12.27], 0.7416		1.81 [0.09, 36.44], 0.6987		2.27 [0.28, 18.21], 0.4394	
OR [95%-CI]; p-value	1.50 [0.14, 16.32], 0.7379		1.89 [0.08, 46.43], 0.6912		2.44 [0.27, 22.34], 0.4182	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7231		0.04 [-0.15, 0.23], 0.6595		0.06 [-0.07, 0.20], 0.3514	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	4/61 (6.6)	9/123 (7.3)	3/63 (4.8)	23/241 (9.5)	7/124 (5.6)
RR [95%-CI]; p-value	1.81 [0.62, 5.26], 0.2762		1.54 [0.43, 5.48], 0.5077		1.69 [0.75, 3.83], 0.2083	
OR [95%-CI]; p-value	1.92 [0.60, 6.10], 0.2631		1.58 [0.41, 6.05], 0.5020		1.76 [0.73, 4.23], 0.1990	
RD [95%-CI]; p-value	0.05 [-0.03, 0.14], 0.2223		0.03 [-0.04, 0.10], 0.4736		0.04 [-0.02, 0.09], 0.1648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2630		0.0899		0.7859	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	7/44 (15.9)	4/20 (20.0)
RR [95%-CI]; p-value	2.39 [0.32, 18.08], 0.3983		0.29 [0.06, 1.43], 0.1272		0.80 [0.26, 2.41], 0.6859	
OR [95%-CI]; p-value	2.78 [0.28, 27.21], 0.3654		0.21 [0.03, 1.57], 0.1088		0.76 [0.19, 2.95], 0.6876	
RD [95%-CI]; p-value	0.13 [-0.11, 0.37], 0.3003		-0.24 [-0.57, 0.09], 0.1606		-0.04 [-0.25, 0.17], 0.6970	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	12/118 (10.2)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	24/241 (10.0)	13/124 (10.5)
RR [95%-CI]; p-value	0.69 [0.31, 1.54], 0.3662		1.54 [0.52, 4.57], 0.4399		0.95 [0.50, 1.80], 0.8747	
OR [95%-CI]; p-value	0.65 [0.26, 1.65], 0.3663		1.59 [0.49, 5.16], 0.4329		0.94 [0.46, 1.93], 0.8748	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.06], 0.3893		0.03 [-0.05, 0.11], 0.4030		-0.01 [-0.07, 0.06], 0.8757	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6851		0.7812		0.9433	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	2/11 (18.2)	3/21 (14.3)	1/9 (11.1)	5/44 (11.4)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.08, 2.96], 0.4279		1.29 [0.15, 10.76], 0.8166		0.76 [0.20, 2.86], 0.6825	
OR [95%-CI]; p-value	0.43 [0.05, 3.53], 0.4219		1.33 [0.12, 14.87], 0.8147		0.73 [0.16, 3.39], 0.6835	
RD [95%-CI]; p-value	-0.09 [-0.35, 0.16], 0.4666		0.03 [-0.22, 0.29], 0.8065		-0.04 [-0.22, 0.15], 0.6960	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	26/118 (22.0)	19/61 (31.1)	22/123 (17.9)	12/63 (19.0)	48/241 (19.9)	31/124 (25.0)
RR [95%-CI]; p-value	0.71 [0.43, 1.17], 0.1786		0.94 [0.50, 1.77], 0.8459		0.80 [0.54, 1.18], 0.2609	
OR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1828		0.93 [0.42, 2.02], 0.8462		0.75 [0.45, 1.25], 0.2641	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.1962		-0.01 [-0.13, 0.11], 0.8474		-0.05 [-0.14, 0.04], 0.2756	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5187		0.1364		0.1410	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	5/11 (45.5)	3/21 (14.3)	4/9 (44.4)	7/44 (15.9)	9/20 (45.0)
RR [95%-CI]; p-value	0.38 [0.13, 1.15], 0.0872		0.32 [0.09, 1.15], 0.0815		0.35 [0.15, 0.81], 0.0146	
OR [95%-CI]; p-value	0.25 [0.05, 1.26], 0.0827		0.21 [0.03, 1.25], 0.0735		0.23 [0.07, 0.76], 0.0127	
RD [95%-CI]; p-value	-0.28 [-0.61, 0.05], 0.0981		-0.30 [-0.66, 0.06], 0.0982		-0.29 [-0.53, -0.05], 0.0191	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	20/118 (16.9)	18/61 (29.5)	19/123 (15.4)	10/63 (15.9)	39/241 (16.2)	28/124 (22.6)
RR [95%-CI]; p-value	0.57 [0.33, 1.00], 0.0509		0.97 [0.48, 1.97], 0.9396		0.72 [0.46, 1.11], 0.1329	
OR [95%-CI]; p-value	0.49 [0.23, 1.01], 0.0515		0.97 [0.42, 2.23], 0.9396		0.66 [0.38, 1.14], 0.1348	
RD [95%-CI]; p-value	-0.13 [-0.26, 0.01], 0.0641		-0.00 [-0.11, 0.11], 0.9398		-0.06 [-0.15, 0.02], 0.1497	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9948		0.0501		0.2189	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	3/44 (6.8)	4/20 (20.0)
RR [95%-CI]; p-value	0.48 [0.03, 6.96], 0.5892		0.29 [0.06, 1.43], 0.1272		0.34 [0.08, 1.38], 0.1321	
OR [95%-CI]; p-value	0.45 [0.03, 8.02], 0.5824		0.21 [0.03, 1.57], 0.1088		0.29 [0.06, 1.46], 0.1173	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6232		-0.24 [-0.57, 0.09], 0.1606		-0.13 [-0.32, 0.06], 0.1750	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	11/118 (9.3)	12/61 (19.7)	18/123 (14.6)	5/63 (7.9)	29/241 (12.0)	17/124 (13.7)
RR [95%-CI]; p-value	0.47 [0.22, 1.01], 0.0533		1.84 [0.72, 4.74], 0.2035		0.88 [0.50, 1.53], 0.6469	
OR [95%-CI]; p-value	0.42 [0.17, 1.02], 0.0498		1.99 [0.70, 5.63], 0.1891		0.86 [0.45, 1.64], 0.6476	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0719		0.07 [-0.02, 0.16], 0.1510		-0.02 [-0.09, 0.06], 0.6533	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4770		0.3543		0.3166	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	5/21 (23.8)	3/9 (33.3)	8/44 (18.2)	6/20 (30.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.71 [0.22, 2.37], 0.5825		0.61 [0.24, 1.52], 0.2845	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.63 [0.11, 3.46], 0.5888		0.52 [0.15, 1.77], 0.2891	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.10 [-0.45, 0.26], 0.6019		-0.12 [-0.35, 0.11], 0.3158	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	15/118 (12.7)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	27/241 (11.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.86 [0.40, 1.85], 0.7032		1.54 [0.52, 4.57], 0.4399		1.07 [0.57, 2.00], 0.8352	
OR [95%-CI]; p-value	0.84 [0.35, 2.05], 0.7039		1.59 [0.49, 5.16], 0.4329		1.08 [0.53, 2.17], 0.8349	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7094		0.03 [-0.05, 0.11], 0.4030		0.01 [-0.06, 0.07], 0.8334	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4758		0.0241		0.0222	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	2/11 (18.2)	0/21 (0.0)	3/9 (33.3)	1/44 (2.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.24 [0.02, 2.36], 0.2208		0.07 [0.00, 1.26], 0.0711		0.09 [0.01, 0.73], 0.0239	
OR [95%-CI]; p-value	0.20 [0.02, 2.55], 0.1834		0.05 [0.00, 1.09], 0.0143		0.07 [0.01, 0.65], 0.0038	
RD [95%-CI]; p-value	-0.14 [-0.38, 0.10], 0.2639		-0.31 [-0.62, 0.00], 0.0533		-0.23 [-0.42, -0.03], 0.0222	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	7/61 (11.5)	15/123 (12.2)	3/63 (4.8)	23/241 (9.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.59 [0.22, 1.55], 0.2857		2.56 [0.77, 8.52], 0.1251		1.18 [0.58, 2.41], 0.6421	
OR [95%-CI]; p-value	0.56 [0.19, 1.63], 0.2825		2.78 [0.77, 9.98], 0.1046		1.20 [0.55, 2.61], 0.6407	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.04], 0.3169		0.07 [-0.00, 0.15], 0.0623		0.01 [-0.05, 0.08], 0.6324	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.1.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9167		0.6331		0.8171	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	1/21 (4.8)	1/9 (11.1)	3/44 (6.8)	2/20 (10.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.43 [0.03, 6.12], 0.5324		0.68 [0.12, 3.77], 0.6606	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.40 [0.02, 7.20], 0.5229		0.66 [0.10, 4.29], 0.6602	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.06 [-0.29, 0.16], 0.5796		-0.03 [-0.18, 0.12], 0.6798	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	13/118 (11.0)	8/61 (13.1)	10/123 (8.1)	6/63 (9.5)	23/241 (9.5)	14/124 (11.3)
RR [95%-CI]; p-value	0.84 [0.37, 1.92], 0.6787		0.85 [0.33, 2.24], 0.7481		0.85 [0.45, 1.58], 0.5999	
OR [95%-CI]; p-value	0.82 [0.32, 2.10], 0.6793		0.84 [0.29, 2.43], 0.7483		0.83 [0.41, 1.67], 0.6005	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.08], 0.6863		-0.01 [-0.10, 0.07], 0.7538		-0.02 [-0.08, 0.05], 0.6090	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_1_m_soc_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.3.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3428		0.6996		0.5170	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	0/23 (0.0)	3/11 (27.3)	2/21 (9.5)	0/9 (0.0)	2/44 (4.5)	3/20 (15.0)
RR [95%-CI]; p-value	0.08 [0.00, 1.43], 0.0855		1.81 [0.09, 36.44], 0.6987		0.30 [0.05, 1.67], 0.1710	
OR [95%-CI]; p-value	0.06 [0.00, 1.29], 0.0226		1.89 [0.08, 46.43], 0.6912		0.27 [0.04, 1.76], 0.1486	
RD [95%-CI]; p-value	-0.25 [-0.52, 0.02], 0.0675		0.04 [-0.15, 0.23], 0.6595		-0.10 [-0.27, 0.06], 0.2230	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	9/61 (14.8)	4/123 (3.3)	0/63 (0.0)	10/241 (4.1)	9/124 (7.3)
RR [95%-CI]; p-value	0.34 [0.13, 0.92], 0.0342		4.13 [0.22, 76.91], 0.3418		0.57 [0.24, 1.37], 0.2099	
OR [95%-CI]; p-value	0.31 [0.10, 0.92], 0.0269		4.24 [0.22, 81.39], 0.2986		0.55 [0.22, 1.40], 0.2054	
RD [95%-CI]; p-value	-0.10 [-0.19, 0.00], 0.0517		0.02 [-0.01, 0.06], 0.2054		-0.03 [-0.08, 0.02], 0.2426	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_3_m_pt_ae10pct_vitd.sas using SAS 9.4

Table 12.4.4.1.3.s8
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2083		0.7775		0.2135	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	0/11 (0.0)	2/21 (9.5)	1/9 (11.1)	4/44 (9.1)	1/20 (5.0)
RR [95%-CI]; p-value	2.00 [0.10, 40.86], 0.6525		0.86 [0.09, 8.30], 0.8941		1.82 [0.22, 15.25], 0.5816	
OR [95%-CI]; p-value	2.10 [0.09, 50.57], 0.6424		0.84 [0.07, 10.66], 0.8943		1.90 [0.20, 18.18], 0.5719	
RD [95%-CI]; p-value	0.04 [-0.12, 0.21], 0.6051		-0.02 [-0.26, 0.22], 0.8971		0.04 [-0.09, 0.17], 0.5305	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	5/118 (4.2)	10/61 (16.4)	5/123 (4.1)	2/63 (3.2)	10/241 (4.1)	12/124 (9.7)
RR [95%-CI]; p-value	0.26 [0.09, 0.72], 0.0099		1.28 [0.26, 6.42], 0.7636		0.43 [0.19, 0.96], 0.0406	
OR [95%-CI]; p-value	0.23 [0.07, 0.69], 0.0054		1.29 [0.24, 6.86], 0.7627		0.40 [0.17, 0.96], 0.0356	
RD [95%-CI]; p-value	-0.12 [-0.22, -0.02], 0.0169		0.01 [-0.05, 0.06], 0.7536		-0.06 [-0.11, 0.00], 0.0609	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_3_m_pt_ae10pct_vitd.sas using SAS 9.4

Table 12.4.8.1.1.s8
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9181		0.3342		0.5003	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	1/9 (11.1)	1/44 (2.3)	1/20 (5.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		0.21 [0.01, 5.70], 0.3536		0.45 [0.03, 6.91], 0.5701	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		0.19 [0.01, 6.25], 0.3062		0.44 [0.03, 7.44], 0.5611	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		-0.09 [-0.30, 0.13], 0.4231		-0.03 [-0.13, 0.08], 0.6113	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	7/118 (5.9)	3/61 (4.9)	5/123 (4.1)	2/63 (3.2)	12/241 (5.0)	5/124 (4.0)
RR [95%-CI]; p-value	1.21 [0.32, 4.50], 0.7802		1.28 [0.26, 6.42], 0.7636		1.23 [0.45, 3.43], 0.6854	
OR [95%-CI]; p-value	1.22 [0.30, 4.89], 0.7795		1.29 [0.24, 6.86], 0.7627		1.25 [0.43, 3.62], 0.6843	
RD [95%-CI]; p-value	0.01 [-0.06, 0.08], 0.7733		0.01 [-0.05, 0.06], 0.7536		0.01 [-0.03, 0.05], 0.6745	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_8_1_1_m_soc_sae5pct_vitd.sas using SAS 9.4

Table 12.4.8.1.2.s8
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_8_1_2_m_pt_sae5pct_vitd.sas using SAS 9.4

Table 12.4.5.1.1.s8
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_5_1_1_m_soc_aeg35pct_vitd.sas using SAS 9.4

Table 12.4.5.1.2.s8
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_5_1_2_m_pt_aeg35pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.6827		0.8454		0.6000	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	1/21 (4.8)	0/9 (0.0)	4/44 (9.1)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.90 [0.03, 24.71], 0.9527		0.61 [0.15, 2.46], 0.4834	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.90 [0.03, 29.35], 0.9527		0.57 [0.11, 2.81], 0.4827	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.01 [-0.17, 0.16], 0.9536		-0.06 [-0.24, 0.12], 0.5154	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	6/61 (9.8)	10/123 (8.1)	4/63 (6.3)	18/241 (7.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.69 [0.25, 1.90], 0.4713		1.28 [0.42, 3.92], 0.6650		0.93 [0.44, 1.95], 0.8394	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4704		1.31 [0.39, 4.34], 0.6631		0.92 [0.41, 2.06], 0.8395	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.4932		0.02 [-0.06, 0.09], 0.6511		-0.01 [-0.06, 0.05], 0.8413	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.8497		0.7577		0.8393	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	3/11 (27.3)	7/21 (33.3)	2/9 (22.2)	12/44 (27.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.80 [0.23, 2.75], 0.7196		1.50 [0.38, 5.87], 0.5601		1.09 [0.44, 2.68], 0.8496	
OR [95%-CI]; p-value	0.74 [0.14, 3.88], 0.7219		1.75 [0.29, 10.74], 0.5428		1.13 [0.34, 3.77], 0.8487	
RD [95%-CI]; p-value	-0.06 [-0.37, 0.26], 0.7286		0.11 [-0.23, 0.45], 0.5197		0.02 [-0.21, 0.25], 0.8470	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	23/118 (19.5)	17/61 (27.9)	19/123 (15.4)	5/63 (7.9)	42/241 (17.4)	22/124 (17.7)
RR [95%-CI]; p-value	0.70 [0.41, 1.21], 0.1989		1.95 [0.76, 4.97], 0.1637		0.98 [0.62, 1.57], 0.9403	
OR [95%-CI]; p-value	0.63 [0.30, 1.29], 0.2022		2.12 [0.75, 5.97], 0.1482		0.98 [0.55, 1.73], 0.9403	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2180		0.08 [-0.02, 0.17], 0.1111		-0.00 [-0.09, 0.08], 0.9405	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.7284		0.0722		0.1454	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	0/21 (0.0)	3/9 (33.3)	2/44 (4.5)	4/20 (20.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.07 [0.00, 1.26], 0.0711		0.23 [0.05, 1.14], 0.0718	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.05 [0.00, 1.09], 0.0143		0.19 [0.03, 1.14], 0.0493	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.31 [-0.62, 0.00], 0.0533		-0.15 [-0.34, 0.03], 0.1030	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	17/118 (14.4)	14/61 (23.0)	17/123 (13.8)	8/63 (12.7)	34/241 (14.1)	22/124 (17.7)
RR [95%-CI]; p-value	0.63 [0.33, 1.19], 0.1515		1.09 [0.50, 2.38], 0.8322		0.80 [0.49, 1.30], 0.3598	
OR [95%-CI]; p-value	0.57 [0.26, 1.24], 0.1522		1.10 [0.45, 2.72], 0.8318		0.76 [0.42, 1.37], 0.3616	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1737		0.01 [-0.09, 0.11], 0.8298		-0.04 [-0.12, 0.04], 0.3752	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.9811		0.4456		0.6764	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	8/23 (34.8)	4/11 (36.4)	5/21 (23.8)	1/9 (11.1)	13/44 (29.5)	5/20 (25.0)
RR [95%-CI]; p-value	0.96 [0.37, 2.50], 0.9278		2.14 [0.29, 15.83], 0.4551		1.18 [0.49, 2.87], 0.7116	
OR [95%-CI]; p-value	0.93 [0.21, 4.18], 0.9281		2.50 [0.25, 25.15], 0.4256		1.26 [0.38, 4.18], 0.7077	
RD [95%-CI]; p-value	-0.02 [-0.36, 0.33], 0.9283		0.13 [-0.15, 0.40], 0.3645		0.05 [-0.19, 0.28], 0.7019	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	30/118 (25.4)	16/61 (26.2)	28/123 (22.8)	15/63 (23.8)	58/241 (24.1)	31/124 (25.0)
RR [95%-CI]; p-value	0.97 [0.58, 1.63], 0.9068		0.96 [0.55, 1.66], 0.8726		0.96 [0.66, 1.41], 0.8437	
OR [95%-CI]; p-value	0.96 [0.47, 1.94], 0.9069		0.94 [0.46, 1.93], 0.8729		0.95 [0.58, 1.57], 0.8440	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.13], 0.9072		-0.01 [-0.14, 0.12], 0.8735		-0.01 [-0.10, 0.08], 0.8447	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.8496		0.9217		0.7953	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	1/11 (9.1)	2/21 (9.5)	0/9 (0.0)	5/44 (11.4)	1/20 (5.0)
RR [95%-CI]; p-value	1.43 [0.17, 12.27], 0.7416		1.81 [0.09, 36.44], 0.6987		2.27 [0.28, 18.21], 0.4394	
OR [95%-CI]; p-value	1.50 [0.14, 16.32], 0.7379		1.89 [0.08, 46.43], 0.6912		2.44 [0.27, 22.34], 0.4182	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7231		0.04 [-0.15, 0.23], 0.6595		0.06 [-0.07, 0.20], 0.3514	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	14/118 (11.9)	4/61 (6.6)	9/123 (7.3)	3/63 (4.8)	23/241 (9.5)	7/124 (5.6)
RR [95%-CI]; p-value	1.81 [0.62, 5.26], 0.2762		1.54 [0.43, 5.48], 0.5077		1.69 [0.75, 3.83], 0.2083	
OR [95%-CI]; p-value	1.92 [0.60, 6.10], 0.2631		1.58 [0.41, 6.05], 0.5020		1.76 [0.73, 4.23], 0.1990	
RD [95%-CI]; p-value	0.05 [-0.03, 0.14], 0.2223		0.03 [-0.04, 0.10], 0.4736		0.04 [-0.02, 0.09], 0.1648	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.2630		0.0899		0.7859	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	5/23 (21.7)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	7/44 (15.9)	4/20 (20.0)
RR [95%-CI]; p-value	2.39 [0.32, 18.08], 0.3983		0.29 [0.06, 1.43], 0.1272		0.80 [0.26, 2.41], 0.6859	
OR [95%-CI]; p-value	2.78 [0.28, 27.21], 0.3654		0.21 [0.03, 1.57], 0.1088		0.76 [0.19, 2.95], 0.6876	
RD [95%-CI]; p-value	0.13 [-0.11, 0.37], 0.3003		-0.24 [-0.57, 0.09], 0.1606		-0.04 [-0.25, 0.17], 0.6970	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	12/118 (10.2)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	24/241 (10.0)	13/124 (10.5)
RR [95%-CI]; p-value	0.69 [0.31, 1.54], 0.3662		1.54 [0.52, 4.57], 0.4399		0.95 [0.50, 1.80], 0.8747	
OR [95%-CI]; p-value	0.65 [0.26, 1.65], 0.3663		1.59 [0.49, 5.16], 0.4329		0.94 [0.46, 1.93], 0.8748	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.06], 0.3893		0.03 [-0.05, 0.11], 0.4030		-0.01 [-0.07, 0.06], 0.8757	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.6851		0.7812		0.9433	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	2/11 (18.2)	3/21 (14.3)	1/9 (11.1)	5/44 (11.4)	3/20 (15.0)
RR [95%-CI]; p-value	0.48 [0.08, 2.96], 0.4279		1.29 [0.15, 10.76], 0.8166		0.76 [0.20, 2.86], 0.6825	
OR [95%-CI]; p-value	0.43 [0.05, 3.53], 0.4219		1.33 [0.12, 14.87], 0.8147		0.73 [0.16, 3.39], 0.6835	
RD [95%-CI]; p-value	-0.09 [-0.35, 0.16], 0.4666		0.03 [-0.22, 0.29], 0.8065		-0.04 [-0.22, 0.15], 0.6960	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	26/118 (22.0)	19/61 (31.1)	22/123 (17.9)	12/63 (19.0)	48/241 (19.9)	31/124 (25.0)
RR [95%-CI]; p-value	0.71 [0.43, 1.17], 0.1786		0.94 [0.50, 1.77], 0.8459		0.80 [0.54, 1.18], 0.2609	
OR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1828		0.93 [0.42, 2.02], 0.8462		0.75 [0.45, 1.25], 0.2641	
RD [95%-CI]; p-value	-0.09 [-0.23, 0.05], 0.1962		-0.01 [-0.13, 0.11], 0.8474		-0.05 [-0.14, 0.04], 0.2756	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5187		0.1364		0.1410	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	5/11 (45.5)	3/21 (14.3)	4/9 (44.4)	7/44 (15.9)	9/20 (45.0)
RR [95%-CI]; p-value	0.38 [0.13, 1.15], 0.0872		0.32 [0.09, 1.15], 0.0815		0.35 [0.15, 0.81], 0.0146	
OR [95%-CI]; p-value	0.25 [0.05, 1.26], 0.0827		0.21 [0.03, 1.25], 0.0735		0.23 [0.07, 0.76], 0.0127	
RD [95%-CI]; p-value	-0.28 [-0.61, 0.05], 0.0981		-0.30 [-0.66, 0.06], 0.0982		-0.29 [-0.53, -0.05], 0.0191	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	20/118 (16.9)	18/61 (29.5)	19/123 (15.4)	10/63 (15.9)	39/241 (16.2)	28/124 (22.6)
RR [95%-CI]; p-value	0.57 [0.33, 1.00], 0.0509		0.97 [0.48, 1.97], 0.9396		0.72 [0.46, 1.11], 0.1329	
OR [95%-CI]; p-value	0.49 [0.23, 1.01], 0.0515		0.97 [0.42, 2.23], 0.9396		0.66 [0.38, 1.14], 0.1348	
RD [95%-CI]; p-value	-0.13 [-0.26, 0.01], 0.0641		-0.00 [-0.11, 0.11], 0.9398		-0.06 [-0.15, 0.02], 0.1497	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.9948		0.0501		0.2189	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	1/11 (9.1)	2/21 (9.5)	3/9 (33.3)	3/44 (6.8)	4/20 (20.0)
RR [95%-CI]; p-value	0.48 [0.03, 6.96], 0.5892		0.29 [0.06, 1.43], 0.1272		0.34 [0.08, 1.38], 0.1321	
OR [95%-CI]; p-value	0.45 [0.03, 8.02], 0.5824		0.21 [0.03, 1.57], 0.1088		0.29 [0.06, 1.46], 0.1173	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6232		-0.24 [-0.57, 0.09], 0.1606		-0.13 [-0.32, 0.06], 0.1750	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	11/118 (9.3)	12/61 (19.7)	18/123 (14.6)	5/63 (7.9)	29/241 (12.0)	17/124 (13.7)
RR [95%-CI]; p-value	0.47 [0.22, 1.01], 0.0533		1.84 [0.72, 4.74], 0.2035		0.88 [0.50, 1.53], 0.6469	
OR [95%-CI]; p-value	0.42 [0.17, 1.02], 0.0498		1.99 [0.70, 5.63], 0.1891		0.86 [0.45, 1.64], 0.6476	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0719		0.07 [-0.02, 0.16], 0.1510		-0.02 [-0.09, 0.06], 0.6533	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.9850		0.4097		0.6641	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	2/21 (9.5)	2/9 (22.2)	3/44 (6.8)	2/20 (10.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		0.43 [0.07, 2.59], 0.3556		0.68 [0.12, 3.77], 0.6606	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		0.37 [0.04, 3.14], 0.3484		0.66 [0.10, 4.29], 0.6602	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		-0.13 [-0.43, 0.17], 0.4055		-0.03 [-0.18, 0.12], 0.6798	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	10/118 (8.5)	5/61 (8.2)	10/123 (8.1)	5/63 (7.9)	20/241 (8.3)	10/124 (8.1)
RR [95%-CI]; p-value	1.03 [0.37, 2.89], 0.9493		1.02 [0.37, 2.87], 0.9634		1.03 [0.50, 2.13], 0.9385	
OR [95%-CI]; p-value	1.04 [0.34, 3.18], 0.9493		1.03 [0.34, 3.14], 0.9634		1.03 [0.47, 2.28], 0.9385	
RD [95%-CI]; p-value	0.00 [-0.08, 0.09], 0.9491		0.00 [-0.08, 0.08], 0.9633		0.00 [-0.06, 0.06], 0.9382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4770		0.3543		0.3166	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	5/21 (23.8)	3/9 (33.3)	8/44 (18.2)	6/20 (30.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.71 [0.22, 2.37], 0.5825		0.61 [0.24, 1.52], 0.2845	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.63 [0.11, 3.46], 0.5888		0.52 [0.15, 1.77], 0.2891	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.10 [-0.45, 0.26], 0.6019		-0.12 [-0.35, 0.11], 0.3158	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	15/118 (12.7)	9/61 (14.8)	12/123 (9.8)	4/63 (6.3)	27/241 (11.2)	13/124 (10.5)
RR [95%-CI]; p-value	0.86 [0.40, 1.85], 0.7032		1.54 [0.52, 4.57], 0.4399		1.07 [0.57, 2.00], 0.8352	
OR [95%-CI]; p-value	0.84 [0.35, 2.05], 0.7039		1.59 [0.49, 5.16], 0.4329		1.08 [0.53, 2.17], 0.8349	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7094		0.03 [-0.05, 0.11], 0.4030		0.01 [-0.06, 0.07], 0.8334	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4758		0.0241		0.0222	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	2/11 (18.2)	0/21 (0.0)	3/9 (33.3)	1/44 (2.3)	5/20 (25.0)
RR [95%-CI]; p-value	0.24 [0.02, 2.36], 0.2208		0.07 [0.00, 1.26], 0.0711		0.09 [0.01, 0.73], 0.0239	
OR [95%-CI]; p-value	0.20 [0.02, 2.55], 0.1834		0.05 [0.00, 1.09], 0.0143		0.07 [0.01, 0.65], 0.0038	
RD [95%-CI]; p-value	-0.14 [-0.38, 0.10], 0.2639		-0.31 [-0.62, 0.00], 0.0533		-0.23 [-0.42, -0.03], 0.0222	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	7/61 (11.5)	15/123 (12.2)	3/63 (4.8)	23/241 (9.5)	10/124 (8.1)
RR [95%-CI]; p-value	0.59 [0.22, 1.55], 0.2857		2.56 [0.77, 8.52], 0.1251		1.18 [0.58, 2.41], 0.6421	
OR [95%-CI]; p-value	0.56 [0.19, 1.63], 0.2825		2.78 [0.77, 9.98], 0.1046		1.20 [0.55, 2.61], 0.6407	
RD [95%-CI]; p-value	-0.05 [-0.14, 0.04], 0.3169		0.07 [-0.00, 0.15], 0.0623		0.01 [-0.05, 0.08], 0.6324	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.2.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.9167		0.6331		0.8171	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	1/11 (9.1)	1/21 (4.8)	1/9 (11.1)	3/44 (6.8)	2/20 (10.0)
RR [95%-CI]; p-value	0.96 [0.10, 9.45], 0.9697		0.43 [0.03, 6.12], 0.5324		0.68 [0.12, 3.77], 0.6606	
OR [95%-CI]; p-value	0.95 [0.08, 11.79], 0.9697		0.40 [0.02, 7.20], 0.5229		0.66 [0.10, 4.29], 0.6602	
RD [95%-CI]; p-value	-0.00 [-0.21, 0.20], 0.9699		-0.06 [-0.29, 0.16], 0.5796		-0.03 [-0.18, 0.12], 0.6798	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	13/118 (11.0)	8/61 (13.1)	10/123 (8.1)	6/63 (9.5)	23/241 (9.5)	14/124 (11.3)
RR [95%-CI]; p-value	0.84 [0.37, 1.92], 0.6787		0.85 [0.33, 2.24], 0.7481		0.85 [0.45, 1.58], 0.5999	
OR [95%-CI]; p-value	0.82 [0.32, 2.10], 0.6793		0.84 [0.29, 2.43], 0.7483		0.83 [0.41, 1.67], 0.6005	
RD [95%-CI]; p-value	-0.02 [-0.12, 0.08], 0.6863		-0.01 [-0.10, 0.07], 0.7538		-0.02 [-0.08, 0.05], 0.6090	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_2_m_soc_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.4.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3428		0.6996		0.5170	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	0/23 (0.0)	3/11 (27.3)	2/21 (9.5)	0/9 (0.0)	2/44 (4.5)	3/20 (15.0)
RR [95%-CI]; p-value	0.08 [0.00, 1.43], 0.0855		1.81 [0.09, 36.44], 0.6987		0.30 [0.05, 1.67], 0.1710	
OR [95%-CI]; p-value	0.06 [0.00, 1.29], 0.0226		1.89 [0.08, 46.43], 0.6912		0.27 [0.04, 1.76], 0.1486	
RD [95%-CI]; p-value	-0.25 [-0.52, 0.02], 0.0675		0.04 [-0.15, 0.23], 0.6595		-0.10 [-0.27, 0.06], 0.2230	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	9/61 (14.8)	4/123 (3.3)	0/63 (0.0)	10/241 (4.1)	9/124 (7.3)
RR [95%-CI]; p-value	0.34 [0.13, 0.92], 0.0342		4.13 [0.22, 76.91], 0.3418		0.57 [0.24, 1.37], 0.2099	
OR [95%-CI]; p-value	0.31 [0.10, 0.92], 0.0269		4.24 [0.22, 81.39], 0.2986		0.55 [0.22, 1.40], 0.2054	
RD [95%-CI]; p-value	-0.10 [-0.19, 0.00], 0.0517		0.02 [-0.01, 0.06], 0.2054		-0.03 [-0.08, 0.02], 0.2426	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_4_m_pt_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.4.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2083		0.7775		0.2135	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	2/23 (8.7)	0/11 (0.0)	2/21 (9.5)	1/9 (11.1)	4/44 (9.1)	1/20 (5.0)
RR [95%-CI]; p-value	2.00 [0.10, 40.86], 0.6525		0.86 [0.09, 8.30], 0.8941		1.82 [0.22, 15.25], 0.5816	
OR [95%-CI]; p-value	2.10 [0.09, 50.57], 0.6424		0.84 [0.07, 10.66], 0.8943		1.90 [0.20, 18.18], 0.5719	
RD [95%-CI]; p-value	0.04 [-0.12, 0.21], 0.6051		-0.02 [-0.26, 0.22], 0.8971		0.04 [-0.09, 0.17], 0.5305	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	5/118 (4.2)	10/61 (16.4)	5/123 (4.1)	2/63 (3.2)	10/241 (4.1)	12/124 (9.7)
RR [95%-CI]; p-value	0.26 [0.09, 0.72], 0.0099		1.28 [0.26, 6.42], 0.7636		0.43 [0.19, 0.96], 0.0406	
OR [95%-CI]; p-value	0.23 [0.07, 0.69], 0.0054		1.29 [0.24, 6.86], 0.7627		0.40 [0.17, 0.96], 0.0356	
RD [95%-CI]; p-value	-0.12 [-0.22, -0.02], 0.0169		0.01 [-0.05, 0.06], 0.7536		-0.06 [-0.11, 0.00], 0.0609	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_4_m_pt_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.4.s8
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.5492		0.8301		0.6494	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	1/11 (9.1)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	1/20 (5.0)
RR [95%-CI]; p-value	0.48 [0.03, 6.96], 0.5892		0.44 [0.01, 20.66], 0.6771		0.45 [0.03, 6.91], 0.5701	
OR [95%-CI]; p-value	0.45 [0.03, 8.02], 0.5824		0.43 [0.01, 23.33], 0.6695		0.44 [0.03, 7.44], 0.5611	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6232		-0.03 [-0.19, 0.13], 0.7114		-0.03 [-0.13, 0.08], 0.6113	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	9/118 (7.6)	4/61 (6.6)	8/123 (6.5)	6/63 (9.5)	17/241 (7.1)	10/124 (8.1)
RR [95%-CI]; p-value	1.16 [0.37, 3.62], 0.7944		0.68 [0.25, 1.88], 0.4610		0.87 [0.41, 1.85], 0.7266	
OR [95%-CI]; p-value	1.18 [0.35, 3.99], 0.7938		0.66 [0.22, 2.00], 0.4600		0.87 [0.38, 1.95], 0.7268	
RD [95%-CI]; p-value	0.01 [-0.07, 0.09], 0.7892		-0.03 [-0.11, 0.05], 0.4841		-0.01 [-0.07, 0.05], 0.7319	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_4_m_pt_ae1pct_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.8350		0.2630		0.5072	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	0/11 (0.0)	2/21 (9.5)	3/9 (33.3)	6/44 (13.6)	3/20 (15.0)
RR [95%-CI]; p-value	4.00 [0.23, 69.39], 0.3410		0.29 [0.06, 1.43], 0.1272		0.91 [0.25, 3.27], 0.8841	
OR [95%-CI]; p-value	4.63 [0.22, 96.08], 0.2835		0.21 [0.03, 1.57], 0.1088		0.89 [0.20, 4.01], 0.8844	
RD [95%-CI]; p-value	0.13 [-0.06, 0.33], 0.1891		-0.24 [-0.57, 0.09], 0.1606		-0.01 [-0.20, 0.17], 0.8860	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	11/118 (9.3)	2/61 (3.3)	7/123 (5.7)	4/63 (6.3)	18/241 (7.5)	6/124 (4.8)
RR [95%-CI]; p-value	2.84 [0.65, 12.42], 0.1649		0.90 [0.27, 2.95], 0.8570		1.54 [0.63, 3.79], 0.3435	
OR [95%-CI]; p-value	3.03 [0.65, 14.14], 0.1398		0.89 [0.25, 3.16], 0.8571		1.59 [0.61, 4.11], 0.3369	
RD [95%-CI]; p-value	0.06 [-0.01, 0.13], 0.0856		-0.01 [-0.08, 0.07], 0.8594		0.03 [-0.02, 0.08], 0.3052	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9863		0.9512		0.9623	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	0/20 (0.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		NA		0.93 [0.03, 26.67], 0.9671	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		NA		0.93 [0.03, 28.89], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		NA		-0.00 [-0.08, 0.08], 0.9675	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	1/118 (0.8)	0/61 (0.0)	1/123 (0.8)	1/63 (1.6)	2/241 (0.8)	1/124 (0.8)
RR [95%-CI]; p-value	1.04 [0.04, 30.64], 0.9808		0.51 [0.03, 8.05], 0.6341		1.03 [0.09, 11.24], 0.9813	
OR [95%-CI]; p-value	1.04 [0.03, 31.52], 0.9808		0.51 [0.03, 8.26], 0.6280		1.03 [0.09, 11.46], 0.9813	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9807		-0.01 [-0.04, 0.03], 0.6619		0.00 [-0.02, 0.02], 0.9812	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9288		0.2339		0.3572	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	0/11 (0.0)	2/21 (9.5)	3/9 (33.3)	5/44 (11.4)	3/20 (15.0)
RR [95%-CI]; p-value	3.00 [0.16, 55.02], 0.4592		0.29 [0.06, 1.43], 0.1272		0.76 [0.20, 2.86], 0.6825	
OR [95%-CI]; p-value	3.30 [0.15, 72.02], 0.4252		0.21 [0.03, 1.57], 0.1088		0.73 [0.16, 3.39], 0.6835	
RD [95%-CI]; p-value	0.09 [-0.09, 0.27], 0.3469		-0.24 [-0.57, 0.09], 0.1606		-0.04 [-0.22, 0.15], 0.6960	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	10/118 (8.5)	2/61 (3.3)	6/123 (4.9)	3/63 (4.8)	16/241 (6.6)	5/124 (4.0)
RR [95%-CI]; p-value	2.58 [0.58, 11.43], 0.2105		1.02 [0.26, 3.96], 0.9721		1.65 [0.62, 4.39], 0.3189	
OR [95%-CI]; p-value	2.73 [0.58, 12.88], 0.1877		1.03 [0.25, 4.24], 0.9721		1.69 [0.61, 4.73], 0.3111	
RD [95%-CI]; p-value	0.05 [-0.02, 0.12], 0.1299		0.00 [-0.06, 0.07], 0.9720		0.03 [-0.02, 0.07], 0.2746	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.5720		0.4326		0.4243	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	0/20 (0.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		NA		0.93 [0.03, 26.67], 0.9671	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		NA		0.93 [0.03, 28.89], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		NA		-0.00 [-0.08, 0.08], 0.9675	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	6/118 (5.1)	1/61 (1.6)	3/123 (2.4)	0/63 (0.0)	9/241 (3.7)	1/124 (0.8)
RR [95%-CI]; p-value	3.10 [0.38, 25.19], 0.2894		3.10 [0.16, 60.90], 0.4569		4.63 [0.59, 36.14], 0.1437	
OR [95%-CI]; p-value	3.21 [0.38, 27.32], 0.2597		3.15 [0.16, 63.87], 0.4309		4.77 [0.60, 38.10], 0.1046	
RD [95%-CI]; p-value	0.03 [-0.02, 0.09], 0.1843		0.02 [-0.02, 0.05], 0.3532		0.03 [0.00, 0.06], 0.0452	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9267		0.2929		0.3004	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	4/23 (17.4)	3/11 (27.3)	0/21 (0.0)	1/9 (11.1)	4/44 (9.1)	4/20 (20.0)
RR [95%-CI]; p-value	0.64 [0.17, 2.37], 0.5019		0.21 [0.01, 5.70], 0.3536		0.45 [0.13, 1.64], 0.2277	
OR [95%-CI]; p-value	0.56 [0.10, 3.10], 0.5050		0.19 [0.01, 6.25], 0.3062		0.40 [0.09, 1.80], 0.2213	
RD [95%-CI]; p-value	-0.10 [-0.40, 0.21], 0.5260		-0.09 [-0.30, 0.13], 0.4231		-0.11 [-0.30, 0.09], 0.2724	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	8/118 (6.8)	6/61 (9.8)	13/123 (10.6)	5/63 (7.9)	21/241 (8.7)	11/124 (8.9)
RR [95%-CI]; p-value	0.69 [0.25, 1.90], 0.4713		1.33 [0.50, 3.57], 0.5689		0.98 [0.49, 1.97], 0.9599	
OR [95%-CI]; p-value	0.67 [0.22, 2.02], 0.4704		1.37 [0.47, 4.03], 0.5655		0.98 [0.46, 2.11], 0.9599	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.4932		0.03 [-0.06, 0.11], 0.5488		-0.00 [-0.06, 0.06], 0.9600	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9863		0.4959		0.6167	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	1/23 (4.3)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	1/44 (2.3)	0/20 (0.0)
RR [95%-CI]; p-value	1.00 [0.04, 27.66], 1.0000		NA		0.93 [0.03, 26.67], 0.9671	
OR [95%-CI]; p-value	1.00 [0.03, 32.17], 1.0000		NA		0.93 [0.03, 28.89], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.14, 0.14], 1.0000		NA		-0.00 [-0.08, 0.08], 0.9675	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	1/118 (0.8)	0/61 (0.0)	4/123 (3.3)	1/63 (1.6)	5/241 (2.1)	1/124 (0.8)
RR [95%-CI]; p-value	1.04 [0.04, 30.64], 0.9808		2.05 [0.23, 17.95], 0.5171		2.57 [0.30, 21.78], 0.3859	
OR [95%-CI]; p-value	1.04 [0.03, 31.52], 0.9808		2.08 [0.23, 19.05], 0.5065		2.61 [0.30, 22.55], 0.3668	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9807		0.02 [-0.03, 0.06], 0.4583		0.01 [-0.01, 0.04], 0.2985	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7975		0.3685		0.2928	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	3/11 (27.3)	0/21 (0.0)	1/9 (11.1)	3/44 (6.8)	4/20 (20.0)
RR [95%-CI]; p-value	0.48 [0.11, 2.00], 0.3120		0.21 [0.01, 5.70], 0.3536		0.34 [0.08, 1.38], 0.1321	
OR [95%-CI]; p-value	0.40 [0.07, 2.42], 0.3086		0.19 [0.01, 6.25], 0.3062		0.29 [0.06, 1.46], 0.1173	
RD [95%-CI]; p-value	-0.14 [-0.44, 0.15], 0.3477		-0.09 [-0.30, 0.13], 0.4231		-0.13 [-0.32, 0.06], 0.1750	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	7/118 (5.9)	6/61 (9.8)	10/123 (8.1)	5/63 (7.9)	17/241 (7.1)	11/124 (8.9)
RR [95%-CI]; p-value	0.60 [0.21, 1.72], 0.3433		1.02 [0.37, 2.87], 0.9634		0.80 [0.38, 1.64], 0.5365	
OR [95%-CI]; p-value	0.58 [0.19, 1.80], 0.3401		1.03 [0.34, 3.14], 0.9634		0.78 [0.35, 1.72], 0.5367	
RD [95%-CI]; p-value	-0.04 [-0.13, 0.05], 0.3738		0.00 [-0.08, 0.08], 0.9633		-0.02 [-0.08, 0.04], 0.5500	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.7.s8
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8664		0.4331		0.8906	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	0/11 (0.0)	0/21 (0.0)	0/9 (0.0)	3/44 (6.8)	0/20 (0.0)
RR [95%-CI]; p-value	3.00 [0.16, 55.02], 0.4592		NA		2.80 [0.15, 53.29], 0.4943	
OR [95%-CI]; p-value	3.30 [0.15, 72.02], 0.4252		NA		2.93 [0.14, 61.26], 0.4697	
RD [95%-CI]; p-value	0.09 [-0.09, 0.27], 0.3469		NA		0.04 [-0.06, 0.14], 0.3909	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	2/118 (1.7)	0/61 (0.0)	5/123 (4.1)	1/63 (1.6)	7/241 (2.9)	1/124 (0.8)
RR [95%-CI]; p-value	2.08 [0.10, 45.52], 0.6405		2.56 [0.31, 21.45], 0.3858		3.60 [0.45, 28.95], 0.2282	
OR [95%-CI]; p-value	2.10 [0.09, 47.37], 0.6323		2.63 [0.30, 22.98], 0.3654		3.68 [0.45, 30.25], 0.1948	
RD [95%-CI]; p-value	0.01 [-0.02, 0.04], 0.5931		0.02 [-0.02, 0.07], 0.2972		0.02 [-0.01, 0.05], 0.1194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_7_m_pt_smq_vitd.sas using SAS 9.4

Table 12.4.4.1.6.s8
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.2955		0.9762		0.5427	
1.Vitamin D Users	N1=23	N1=11	N1=21	N1=9	N1=44	N1=20
n/N1 (%)	3/23 (13.0)	4/11 (36.4)	7/21 (33.3)	2/9 (22.2)	10/44 (22.7)	6/20 (30.0)
RR [95%-CI]; p-value	0.36 [0.10, 1.33], 0.1260		1.50 [0.38, 5.87], 0.5601		0.76 [0.32, 1.80], 0.5284	
OR [95%-CI]; p-value	0.26 [0.05, 1.48], 0.1157		1.75 [0.29, 10.74], 0.5428		0.69 [0.21, 2.25], 0.5334	
RD [95%-CI]; p-value	-0.23 [-0.55, 0.08], 0.1479		0.11 [-0.23, 0.45], 0.5197		-0.07 [-0.31, 0.16], 0.5457	
2.non-Vitamin D Users	N2=118	N2=61	N2=123	N2=63	N2=241	N2=124
n/N2 (%)	21/118 (17.8)	14/61 (23.0)	21/123 (17.1)	7/63 (11.1)	42/241 (17.4)	21/124 (16.9)
RR [95%-CI]; p-value	0.78 [0.42, 1.42], 0.4072		1.54 [0.69, 3.42], 0.2924		1.03 [0.64, 1.66], 0.9063	
OR [95%-CI]; p-value	0.73 [0.34, 1.56], 0.4099		1.65 [0.66, 4.11], 0.2819		1.04 [0.58, 1.84], 0.9062	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4230		0.06 [-0.04, 0.16], 0.2529		0.00 [-0.08, 0.09], 0.9059	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd/T12_4_4_1_6_m_pt_adr_vitd.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE						
Interaction p-value	0.8075		0.9529		0.7492	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	53/68 (77.9)	34/40 (85.0)	46/70 (65.7)	23/36 (63.9)	99/138 (71.7)	57/76 (75.0)
RR [95%-CI]; p-value	0.92 [0.76, 1.10], 0.3491		1.03 [0.76, 1.39], 0.8531		0.96 [0.81, 1.13], 0.6014	
OR [95%-CI]; p-value	0.62 [0.22, 1.76], 0.3707		1.08 [0.47, 2.51], 0.8519		0.85 [0.45, 1.60], 0.6075	
RD [95%-CI]; p-value	-0.07 [-0.22, 0.08], 0.3505		0.02 [-0.17, 0.21], 0.8524		-0.03 [-0.16, 0.09], 0.6032	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	48/73 (65.8)	22/32 (68.8)	45/74 (60.8)	21/36 (58.3)	93/147 (63.3)	43/68 (63.2)
RR [95%-CI]; p-value	0.96 [0.72, 1.27], 0.7603		1.04 [0.75, 1.45], 0.8056		1.00 [0.80, 1.25], 0.9966	
OR [95%-CI]; p-value	0.87 [0.36, 2.13], 0.7643		1.11 [0.49, 2.49], 0.8035		1.00 [0.55, 1.82], 0.9966	
RD [95%-CI]; p-value	-0.03 [-0.22, 0.16], 0.7621		0.02 [-0.17, 0.22], 0.8041		0.00 [-0.14, 0.14], 0.9966	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with drug-related AE						
Interaction p-value	0.5179		0.9728		0.8309	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	10/68 (14.7)	6/40 (15.0)	9/70 (12.9)	1/36 (2.8)	19/138 (13.8)	7/76 (9.2)
RR [95%-CI]; p-value	0.98 [0.39, 2.49], 0.9668		4.63 [0.61, 35.12], 0.1384		1.49 [0.66, 3.39], 0.3367	
OR [95%-CI]; p-value	0.98 [0.33, 2.93], 0.9669		5.16 [0.63, 42.48], 0.0927		1.57 [0.63, 3.93], 0.3288	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.14], 0.9669		0.10 [0.01, 0.20], 0.0376		0.05 [-0.04, 0.13], 0.3033	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	5/32 (15.6)	10/74 (13.5)	1/36 (2.8)	17/147 (11.6)	6/68 (8.8)
RR [95%-CI]; p-value	0.61 [0.21, 1.79], 0.3710		4.86 [0.65, 36.55], 0.1242		1.31 [0.54, 3.18], 0.5492	
OR [95%-CI]; p-value	0.57 [0.17, 1.96], 0.3709		5.47 [0.67, 44.50], 0.0782		1.35 [0.51, 3.60], 0.5454	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.08], 0.4074		0.11 [0.01, 0.20], 0.0261		0.03 [-0.06, 0.11], 0.5271	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with severe AE						
Interaction p-value	0.1281		0.7175		0.3731	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	5/40 (12.5)	5/70 (7.1)	3/36 (8.3)	12/138 (8.7)	8/76 (10.5)
RR [95%-CI]; p-value	0.82 [0.28, 2.42], 0.7244		0.86 [0.22, 3.39], 0.8259		0.83 [0.35, 1.93], 0.6594	
OR [95%-CI]; p-value	0.80 [0.24, 2.72], 0.7246		0.85 [0.19, 3.76], 0.8261		0.81 [0.32, 2.08], 0.6597	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.10], 0.7302		-0.01 [-0.12, 0.10], 0.8299		-0.02 [-0.10, 0.07], 0.6674	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	11/73 (15.1)	1/32 (3.1)	5/74 (6.8)	4/36 (11.1)	16/147 (10.9)	5/68 (7.4)
RR [95%-CI]; p-value	4.82 [0.65, 35.79], 0.1240		0.61 [0.17, 2.13], 0.4365		1.48 [0.57, 3.87], 0.4243	
OR [95%-CI]; p-value	5.50 [0.68, 44.56], 0.0766		0.58 [0.15, 2.30], 0.4343		1.54 [0.54, 4.39], 0.4173	
RD [95%-CI]; p-value	0.12 [0.02, 0.22], 0.0215		-0.04 [-0.16, 0.07], 0.4677		0.04 [-0.04, 0.12], 0.3863	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with SAE						
Interaction p-value	0.9668		0.6509		0.7528	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	13/68 (19.1)	6/40 (15.0)	10/70 (14.3)	6/36 (16.7)	23/138 (16.7)	12/76 (15.8)
RR [95%-CI]; p-value	1.27 [0.53, 3.09], 0.5911		0.86 [0.34, 2.17], 0.7450		1.06 [0.56, 2.00], 0.8684	
OR [95%-CI]; p-value	1.34 [0.47, 3.86], 0.5873		0.83 [0.28, 2.51], 0.7457		1.07 [0.50, 2.29], 0.8681	
RD [95%-CI]; p-value	0.04 [-0.10, 0.19], 0.5774		-0.02 [-0.17, 0.12], 0.7505		0.01 [-0.09, 0.11], 0.8673	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	17/73 (23.3)	6/32 (18.8)	12/74 (16.2)	5/36 (13.9)	29/147 (19.7)	11/68 (16.2)
RR [95%-CI]; p-value	1.24 [0.54, 2.86], 0.6100		1.17 [0.45, 3.06], 0.7528		1.22 [0.65, 2.29], 0.5380	
OR [95%-CI]; p-value	1.32 [0.46, 3.72], 0.6048		1.20 [0.39, 3.71], 0.7514		1.27 [0.59, 2.73], 0.5338	
RD [95%-CI]; p-value	0.05 [-0.12, 0.21], 0.5930		0.02 [-0.12, 0.16], 0.7459		0.04 [-0.07, 0.14], 0.5216	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.0281		0.9429		0.0354	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	5/40 (12.5)	7/70 (10.0)	2/36 (5.6)	10/138 (7.2)	7/76 (9.2)
RR [95%-CI]; p-value	0.35 [0.09, 1.40], 0.1383		1.80 [0.39, 8.22], 0.4483		0.79 [0.31, 1.98], 0.6111	
OR [95%-CI]; p-value	0.32 [0.07, 1.43], 0.1212		1.89 [0.37, 9.60], 0.4369		0.77 [0.28, 2.11], 0.6111	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.03], 0.1626		0.04 [-0.06, 0.15], 0.3961		-0.02 [-0.10, 0.06], 0.6220	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	13/73 (17.8)	0/32 (0.0)	8/74 (10.8)	2/36 (5.6)	21/147 (14.3)	2/68 (2.9)
RR [95%-CI]; p-value	11.58 [0.71, 189.25], 0.0858		1.95 [0.44, 8.70], 0.3835		4.86 [1.17, 20.13], 0.0293	
OR [95%-CI]; p-value	13.87 [0.80, 241.41], 0.0209		2.06 [0.41, 10.24], 0.3683		5.50 [1.25, 24.18], 0.0123	
RD [95%-CI]; p-value	0.16 [0.07, 0.26], 0.0011		0.05 [-0.05, 0.16], 0.3172		0.11 [0.04, 0.18], 0.0013	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.2089		0.5129		0.1208	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	2/68 (2.9)	2/40 (5.0)	3/70 (4.3)	2/36 (5.6)	5/138 (3.6)	4/76 (5.3)
RR [95%-CI]; p-value	0.59 [0.09, 4.01], 0.5882		0.77 [0.13, 4.41], 0.7705		0.69 [0.19, 2.49], 0.5689	
OR [95%-CI]; p-value	0.58 [0.08, 4.26], 0.5843		0.76 [0.12, 4.77], 0.7702		0.68 [0.18, 2.60], 0.5673	
RD [95%-CI]; p-value	-0.02 [-0.10, 0.06], 0.6076		-0.01 [-0.10, 0.08], 0.7788		-0.02 [-0.08, 0.04], 0.5865	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	0/32 (0.0)	4/74 (5.4)	1/36 (2.8)	10/147 (6.8)	1/68 (1.5)
RR [95%-CI]; p-value	5.34 [0.31, 92.84], 0.2500		1.95 [0.23, 16.79], 0.5448		4.63 [0.60, 35.41], 0.1402	
OR [95%-CI]; p-value	5.73 [0.31, 105.80], 0.1876		2.00 [0.22, 18.57], 0.5347		4.89 [0.61, 39.00], 0.0989	
RD [95%-CI]; p-value	0.07 [-0.01, 0.14], 0.0845		0.03 [-0.05, 0.10], 0.4888		0.05 [0.00, 0.10], 0.0357	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE leading to death						
Interaction p-value	0.3340		0.5223		0.1392	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	0/68 (0.0)	1/40 (2.5)	1/70 (1.4)	1/36 (2.8)	1/138 (0.7)	2/76 (2.6)
RR [95%-CI]; p-value	0.29 [0.01, 8.51], 0.4743		0.51 [0.03, 7.98], 0.6346		0.28 [0.03, 2.99], 0.2890	
OR [95%-CI]; p-value	0.29 [0.01, 8.74], 0.4462		0.51 [0.03, 8.35], 0.6287		0.27 [0.02, 3.03], 0.2562	
RD [95%-CI]; p-value	-0.02 [-0.07, 0.03], 0.5080		-0.01 [-0.07, 0.05], 0.6618		-0.02 [-0.06, 0.02], 0.3338	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	0/32 (0.0)	2/74 (2.7)	0/36 (0.0)	5/147 (3.4)	0/68 (0.0)
RR [95%-CI]; p-value	2.67 [0.14, 51.82], 0.5161		1.97 [0.09, 42.65], 0.6648		4.66 [0.26, 84.09], 0.2971	
OR [95%-CI]; p-value	2.74 [0.13, 56.37], 0.4960		2.00 [0.09, 45.51], 0.6577		4.79 [0.26, 88.92], 0.2469	
RD [95%-CI]; p-value	0.03 [-0.04, 0.09], 0.4176		0.01 [-0.04, 0.07], 0.6207		0.03 [-0.01, 0.06], 0.1410	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.9990		0.1832		0.4295	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	45/68 (66.2)	31/40 (77.5)	36/70 (51.4)	15/36 (41.7)	81/138 (58.7)	46/76 (60.5)
RR [95%-CI]; p-value	0.85 [0.67, 1.08], 0.1938		1.23 [0.79, 1.93], 0.3577		0.97 [0.77, 1.22], 0.7929	
OR [95%-CI]; p-value	0.57 [0.23, 1.39], 0.2133		1.48 [0.66, 3.34], 0.3408		0.93 [0.52, 1.64], 0.7942	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.06], 0.1955		0.10 [-0.10, 0.30], 0.3366		-0.02 [-0.16, 0.12], 0.7937	
2.Baseline 25D ≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	37/73 (50.7)	19/32 (59.4)	34/74 (45.9)	20/36 (55.6)	71/147 (48.3)	39/68 (57.4)
RR [95%-CI]; p-value	0.85 [0.59, 1.23], 0.3957		0.83 [0.56, 1.21], 0.3307		0.84 [0.65, 1.10], 0.2030	
OR [95%-CI]; p-value	0.70 [0.30, 1.63], 0.4113		0.68 [0.31, 1.51], 0.3442		0.69 [0.39, 1.24], 0.2168	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.12], 0.4065		-0.10 [-0.29, 0.10], 0.3417		-0.09 [-0.23, 0.05], 0.2135	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Moderate						
Interaction p-value	0.8138		0.6592		0.8382	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	25/68 (36.8)	16/40 (40.0)	24/70 (34.3)	10/36 (27.8)	49/138 (35.5)	26/76 (34.2)
RR [95%-CI]; p-value	0.92 [0.56, 1.50], 0.7364		1.23 [0.66, 2.29], 0.5048		1.04 [0.71, 1.52], 0.8496	
OR [95%-CI]; p-value	0.87 [0.39, 1.94], 0.7380		1.36 [0.56, 3.27], 0.4966		1.06 [0.59, 1.91], 0.8491	
RD [95%-CI]; p-value	-0.03 [-0.22, 0.16], 0.7389		0.07 [-0.12, 0.25], 0.4876		0.01 [-0.12, 0.15], 0.8487	
2.Baseline 25D ≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	25/73 (34.2)	13/32 (40.6)	25/74 (33.8)	8/36 (22.2)	50/147 (34.0)	21/68 (30.9)
RR [95%-CI]; p-value	0.84 [0.50, 1.43], 0.5244		1.52 [0.76, 3.03], 0.2337		1.10 [0.72, 1.68], 0.6529	
OR [95%-CI]; p-value	0.76 [0.32, 1.79], 0.5313		1.79 [0.71, 4.49], 0.2144		1.15 [0.62, 2.14], 0.6498	
RD [95%-CI]; p-value	-0.06 [-0.27, 0.14], 0.5360		0.12 [-0.06, 0.29], 0.1912		0.03 [-0.10, 0.17], 0.6467	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.3.1.s9
Overall Summary of Treatment-Emergent Adverse Events
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Severe						
Interaction p-value	0.1281		0.7175		0.3731	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	5/40 (12.5)	5/70 (7.1)	3/36 (8.3)	12/138 (8.7)	8/76 (10.5)
RR [95%-CI]; p-value	0.82 [0.28, 2.42], 0.7244		0.86 [0.22, 3.39], 0.8259		0.83 [0.35, 1.93], 0.6594	
OR [95%-CI]; p-value	0.80 [0.24, 2.72], 0.7246		0.85 [0.19, 3.76], 0.8261		0.81 [0.32, 2.08], 0.6597	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.10], 0.7302		-0.01 [-0.12, 0.10], 0.8299		-0.02 [-0.10, 0.07], 0.6674	
2.Baseline 25D ≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	11/73 (15.1)	1/32 (3.1)	5/74 (6.8)	4/36 (11.1)	16/147 (10.9)	5/68 (7.4)
RR [95%-CI]; p-value	4.82 [0.65, 35.79], 0.1240		0.61 [0.17, 2.13], 0.4365		1.48 [0.57, 3.87], 0.4243	
OR [95%-CI]; p-value	5.50 [0.68, 44.56], 0.0766		0.58 [0.15, 2.30], 0.4343		1.54 [0.54, 4.39], 0.4173	
RD [95%-CI]; p-value	0.12 [0.02, 0.22], 0.0215		-0.04 [-0.16, 0.07], 0.4677		0.04 [-0.04, 0.12], 0.3863	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_3_1_m_sf_ttl_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1195		0.4984		0.1099	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	6/70 (8.6)	3/36 (8.3)	10/138 (7.2)	10/76 (13.2)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.03 [0.27, 3.87], 0.9668		0.55 [0.24, 1.26], 0.1593	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.03 [0.24, 4.39], 0.9668		0.52 [0.20, 1.30], 0.1551	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.00 [-0.11, 0.11], 0.9666		-0.06 [-0.15, 0.03], 0.1852	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	2/32 (6.3)	5/74 (6.8)	1/36 (2.8)	12/147 (8.2)	3/68 (4.4)
RR [95%-CI]; p-value	1.53 [0.34, 6.98], 0.5799		2.43 [0.29, 20.06], 0.4089		1.85 [0.54, 6.34], 0.3276	
OR [95%-CI]; p-value	1.59 [0.31, 8.12], 0.5737		2.54 [0.29, 22.55], 0.3885		1.93 [0.53, 7.06], 0.3153	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5434		0.04 [-0.04, 0.12], 0.3201		0.04 [-0.03, 0.10], 0.2645	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6434		0.4204		0.4477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	15/68 (22.1)	11/40 (27.5)	15/70 (21.4)	3/36 (8.3)	30/138 (21.7)	14/76 (18.4)
RR [95%-CI]; p-value	0.80 [0.41, 1.57], 0.5208		2.57 [0.80, 8.31], 0.1144		1.18 [0.67, 2.09], 0.5685	
OR [95%-CI]; p-value	0.75 [0.30, 1.84], 0.5230		3.00 [0.81, 11.15], 0.0890		1.23 [0.61, 2.49], 0.5655	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5302		0.13 [-0.00, 0.26], 0.0516		0.03 [-0.08, 0.14], 0.5581	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	13/73 (17.8)	9/32 (28.1)	11/74 (14.9)	4/36 (11.1)	24/147 (16.3)	13/68 (19.1)
RR [95%-CI]; p-value	0.63 [0.30, 1.33], 0.2270		1.34 [0.46, 3.91], 0.5949		0.85 [0.46, 1.57], 0.6125	
OR [95%-CI]; p-value	0.55 [0.21, 1.47], 0.2318		1.40 [0.41, 4.74], 0.5904		0.83 [0.39, 1.74], 0.6141	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2581		0.04 [-0.09, 0.17], 0.5738		-0.03 [-0.14, 0.08], 0.6219	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1769		0.7513		0.2112	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	9/68 (13.2)	5/40 (12.5)	10/70 (14.3)	6/36 (16.7)	19/138 (13.8)	11/76 (14.5)
RR [95%-CI]; p-value	1.06 [0.38, 2.94], 0.9126		0.86 [0.34, 2.17], 0.7450		0.95 [0.48, 1.89], 0.8867	
OR [95%-CI]; p-value	1.07 [0.33, 3.44], 0.9125		0.83 [0.28, 2.51], 0.7457		0.94 [0.42, 2.10], 0.8869	
RD [95%-CI]; p-value	0.01 [-0.12, 0.14], 0.9120		-0.02 [-0.17, 0.12], 0.7505		-0.01 [-0.10, 0.09], 0.8875	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	10/32 (31.3)	7/74 (9.5)	5/36 (13.9)	17/147 (11.6)	15/68 (22.1)
RR [95%-CI]; p-value	0.44 [0.20, 0.95], 0.0362		0.68 [0.23, 2.00], 0.4843		0.52 [0.28, 0.99], 0.0452	
OR [95%-CI]; p-value	0.35 [0.13, 0.95], 0.0350		0.65 [0.19, 2.20], 0.4844		0.46 [0.22, 0.99], 0.0444	
RD [95%-CI]; p-value	-0.18 [-0.35, 0.00], 0.0545		-0.04 [-0.18, 0.09], 0.5081		-0.10 [-0.22, 0.01], 0.0646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1286		0.1763		0.0462	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	23/68 (33.8)	10/40 (25.0)	20/70 (28.6)	7/36 (19.4)	43/138 (31.2)	17/76 (22.4)
RR [95%-CI]; p-value	1.35 [0.72, 2.54], 0.3481		1.47 [0.69, 3.15], 0.3217		1.39 [0.86, 2.27], 0.1820	
OR [95%-CI]; p-value	1.53 [0.64, 3.68], 0.3364		1.66 [0.63, 4.39], 0.3071		1.57 [0.82, 3.01], 0.1707	
RD [95%-CI]; p-value	0.09 [-0.09, 0.26], 0.3233		0.09 [-0.08, 0.26], 0.2843		0.09 [-0.03, 0.21], 0.1560	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	15/73 (20.5)	10/32 (31.3)	13/74 (17.6)	9/36 (25.0)	28/147 (19.0)	19/68 (27.9)
RR [95%-CI]; p-value	0.66 [0.33, 1.30], 0.2295		0.70 [0.33, 1.49], 0.3570		0.68 [0.41, 1.13], 0.1383	
OR [95%-CI]; p-value	0.57 [0.22, 1.45], 0.2359		0.64 [0.24, 1.67], 0.3605		0.61 [0.31, 1.19], 0.1423	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.08], 0.2580		-0.07 [-0.24, 0.09], 0.3799		-0.09 [-0.21, 0.04], 0.1602	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.2221		0.2372		0.0870	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	4/40 (10.0)	3/70 (4.3)	2/36 (5.6)	10/138 (7.2)	6/76 (7.9)
RR [95%-CI]; p-value	1.03 [0.32, 3.30], 0.9611		0.77 [0.13, 4.41], 0.7705		0.92 [0.35, 2.43], 0.8629	
OR [95%-CI]; p-value	1.03 [0.28, 3.77], 0.9611		0.76 [0.12, 4.77], 0.7702		0.91 [0.32, 2.61], 0.8630	
RD [95%-CI]; p-value	0.00 [-0.11, 0.12], 0.9609		-0.01 [-0.10, 0.08], 0.7788		-0.01 [-0.08, 0.07], 0.8645	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	1/32 (3.1)	8/74 (10.8)	1/36 (2.8)	18/147 (12.2)	2/68 (2.9)
RR [95%-CI]; p-value	4.38 [0.59, 32.82], 0.1502		3.89 [0.51, 29.94], 0.1918		4.16 [0.99, 17.44], 0.0510	
OR [95%-CI]; p-value	4.92 [0.60, 40.19], 0.1034		4.24 [0.51, 35.30], 0.1492		4.60 [1.04, 20.45], 0.0290	
RD [95%-CI]; p-value	0.11 [0.01, 0.21], 0.0368		0.08 [-0.01, 0.17], 0.0763		0.09 [0.03, 0.16], 0.0061	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5193		0.6986		0.5039	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	7/70 (10.0)	3/36 (8.3)	18/138 (13.0)	9/76 (11.8)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		1.20 [0.33, 4.37], 0.7820		1.10 [0.52, 2.33], 0.8005	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		1.22 [0.30, 5.04], 0.7810		1.12 [0.48, 2.62], 0.8000	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.02 [-0.10, 0.13], 0.7753		0.01 [-0.08, 0.10], 0.7976	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	4/32 (12.5)	7/74 (9.5)	4/36 (11.1)	13/147 (8.8)	8/68 (11.8)
RR [95%-CI]; p-value	0.66 [0.20, 2.17], 0.4917		0.85 [0.27, 2.72], 0.7861		0.75 [0.33, 1.73], 0.5016	
OR [95%-CI]; p-value	0.63 [0.16, 2.39], 0.4915		0.84 [0.23, 3.06], 0.7864		0.73 [0.29, 1.85], 0.5023	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5211		-0.02 [-0.14, 0.11], 0.7914		-0.03 [-0.12, 0.06], 0.5213	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.3592		0.7852		0.3259	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	18/68 (26.5)	17/40 (42.5)	14/70 (20.0)	8/36 (22.2)	32/138 (23.2)	25/76 (32.9)
RR [95%-CI]; p-value	0.62 [0.36, 1.06], 0.0832		0.90 [0.42, 1.94], 0.7886		0.70 [0.45, 1.10], 0.1210	
OR [95%-CI]; p-value	0.49 [0.21, 1.11], 0.0857		0.88 [0.33, 2.33], 0.7893		0.62 [0.33, 1.15], 0.1243	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.03], 0.0906		-0.02 [-0.19, 0.14], 0.7918		-0.10 [-0.22, 0.03], 0.1340	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	4/32 (12.5)	11/74 (14.9)	5/36 (13.9)	21/147 (14.3)	9/68 (13.2)
RR [95%-CI]; p-value	1.10 [0.37, 3.24], 0.8683		1.07 [0.40, 2.85], 0.8919		1.08 [0.52, 2.23], 0.8367	
OR [95%-CI]; p-value	1.11 [0.32, 3.85], 0.8679		1.08 [0.35, 3.39], 0.8916		1.09 [0.47, 2.53], 0.8362	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8659		0.01 [-0.13, 0.15], 0.8906		0.01 [-0.09, 0.11], 0.8343	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0583		0.3407		0.0358	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	15/40 (37.5)	9/70 (12.9)	8/36 (22.2)	17/138 (12.3)	23/76 (30.3)
RR [95%-CI]; p-value	0.31 [0.15, 0.67], 0.0029		0.58 [0.24, 1.37], 0.2142		0.41 [0.23, 0.71], 0.0017	
OR [95%-CI]; p-value	0.22 [0.08, 0.59], 0.0016		0.52 [0.18, 1.48], 0.2134		0.32 [0.16, 0.66], 0.0013	
RD [95%-CI]; p-value	-0.26 [-0.43, -0.09], 0.0027		-0.09 [-0.25, 0.06], 0.2418		-0.18 [-0.30, -0.06], 0.0026	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	16/73 (21.9)	8/32 (25.0)	13/74 (17.6)	6/36 (16.7)	29/147 (19.7)	14/68 (20.6)
RR [95%-CI]; p-value	0.88 [0.42, 1.84], 0.7275		1.05 [0.44, 2.55], 0.9068		0.96 [0.54, 1.69], 0.8832	
OR [95%-CI]; p-value	0.84 [0.32, 2.23], 0.7292		1.07 [0.37, 3.08], 0.9066		0.95 [0.46, 1.94], 0.8834	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7336		0.01 [-0.14, 0.16], 0.9060		-0.01 [-0.12, 0.11], 0.8841	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.4751		0.9511		0.8297	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	12/70 (17.1)	5/36 (13.9)	16/138 (11.6)	12/76 (15.8)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.23 [0.47, 3.23], 0.6683		0.73 [0.37, 1.47], 0.3832	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.28 [0.41, 3.97], 0.6655		0.70 [0.31, 1.57], 0.3838	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.03 [-0.11, 0.18], 0.6565		-0.04 [-0.14, 0.06], 0.4007	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	8/73 (11.0)	6/32 (18.8)	8/74 (10.8)	3/36 (8.3)	16/147 (10.9)	9/68 (13.2)
RR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2796		1.30 [0.37, 4.60], 0.6869		0.82 [0.38, 1.77], 0.6161	
OR [95%-CI]; p-value	0.53 [0.17, 1.69], 0.2797		1.33 [0.33, 5.36], 0.6844		0.80 [0.33, 1.92], 0.6170	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.08], 0.3184		0.02 [-0.09, 0.14], 0.6720		-0.02 [-0.12, 0.07], 0.6276	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.2828		0.2380		0.1477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	9/70 (12.9)	2/36 (5.6)	20/138 (14.5)	8/76 (10.5)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		2.31 [0.53, 10.15], 0.2660		1.38 [0.64, 2.98], 0.4161	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		2.51 [0.51, 12.28], 0.2431		1.44 [0.60, 3.45], 0.4103	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.07 [-0.04, 0.18], 0.1867		0.04 [-0.05, 0.13], 0.3909	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	6/32 (18.8)	8/74 (10.8)	5/36 (13.9)	15/147 (10.2)	11/68 (16.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.40], 0.1923		0.78 [0.27, 2.21], 0.6381		0.63 [0.31, 1.30], 0.2116	
OR [95%-CI]; p-value	0.46 [0.14, 1.50], 0.1895		0.75 [0.23, 2.49], 0.6389		0.59 [0.25, 1.36], 0.2117	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.06], 0.2349		-0.03 [-0.16, 0.10], 0.6508		-0.06 [-0.16, 0.04], 0.2431	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4122		0.5245		0.3607	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	5/68 (7.4)	4/40 (10.0)	7/70 (10.0)	2/36 (5.6)	12/138 (8.7)	6/76 (7.9)
RR [95%-CI]; p-value	0.74 [0.21, 2.58], 0.6312		1.80 [0.39, 8.22], 0.4483		1.10 [0.43, 2.82], 0.8402	
OR [95%-CI]; p-value	0.71 [0.18, 2.83], 0.6308		1.89 [0.37, 9.60], 0.4369		1.11 [0.40, 3.09], 0.8399	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.09], 0.6425		0.04 [-0.06, 0.15], 0.3961		0.01 [-0.07, 0.08], 0.8379	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	4/73 (5.5)	5/32 (15.6)	8/74 (10.8)	4/36 (11.1)	12/147 (8.2)	9/68 (13.2)
RR [95%-CI]; p-value	0.35 [0.10, 1.22], 0.0997		0.97 [0.31, 3.02], 0.9622		0.62 [0.27, 1.39], 0.2452	
OR [95%-CI]; p-value	0.31 [0.08, 1.25], 0.0874		0.97 [0.27, 3.46], 0.9622		0.58 [0.23, 1.46], 0.2440	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.03], 0.1443		-0.00 [-0.13, 0.12], 0.9623		-0.05 [-0.14, 0.04], 0.2794	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.1.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7480		0.7289		0.9661	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	6/40 (15.0)	7/70 (10.0)	4/36 (11.1)	15/138 (10.9)	10/76 (13.2)
RR [95%-CI]; p-value	0.78 [0.29, 2.10], 0.6284		0.90 [0.28, 2.87], 0.8588		0.83 [0.39, 1.75], 0.6174	
OR [95%-CI]; p-value	0.76 [0.24, 2.36], 0.6288		0.89 [0.24, 3.26], 0.8590		0.80 [0.34, 1.89], 0.6180	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.10], 0.6375		-0.01 [-0.14, 0.11], 0.8610		-0.02 [-0.11, 0.07], 0.6261	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	3/32 (9.4)	4/74 (5.4)	3/36 (8.3)	11/147 (7.5)	6/68 (8.8)
RR [95%-CI]; p-value	1.02 [0.28, 3.70], 0.9726		0.65 [0.15, 2.75], 0.5566		0.85 [0.33, 2.20], 0.7345	
OR [95%-CI]; p-value	1.03 [0.25, 4.25], 0.9726		0.63 [0.13, 2.97], 0.5550		0.84 [0.30, 2.36], 0.7348	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9725		-0.03 [-0.13, 0.07], 0.5809		-0.01 [-0.09, 0.07], 0.7417	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_1_m_soc_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.3.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9649		0.7289		0.8279	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	7/40 (17.5)	4/70 (5.7)	0/36 (0.0)	7/138 (5.1)	7/76 (9.2)
RR [95%-CI]; p-value	0.25 [0.07, 0.92], 0.0370		4.17 [0.23, 76.77], 0.3365		0.55 [0.20, 1.51], 0.2468	
OR [95%-CI]; p-value	0.22 [0.05, 0.90], 0.0234		4.36 [0.22, 84.87], 0.2902		0.53 [0.18, 1.56], 0.2414	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.00], 0.0442		0.04 [-0.02, 0.11], 0.1982		-0.04 [-0.12, 0.03], 0.2770	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	5/32 (15.6)	2/74 (2.7)	0/36 (0.0)	5/147 (3.4)	5/68 (7.4)
RR [95%-CI]; p-value	0.26 [0.07, 1.03], 0.0560		1.97 [0.09, 42.65], 0.6648		0.46 [0.14, 1.54], 0.2102	
OR [95%-CI]; p-value	0.23 [0.05, 1.04], 0.0406		2.00 [0.09, 45.51], 0.6577		0.44 [0.12, 1.59], 0.2007	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0916		0.01 [-0.04, 0.07], 0.6207		-0.04 [-0.11, 0.03], 0.2590	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_3_m_pt_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.3.s9
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.8538		0.9083		0.7206	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	6/40 (15.0)	2/70 (2.9)	1/36 (2.8)	6/138 (4.3)	7/76 (9.2)
RR [95%-CI]; p-value	0.39 [0.12, 1.31], 0.1273		1.03 [0.10, 10.97], 0.9814		0.47 [0.16, 1.35], 0.1627	
OR [95%-CI]; p-value	0.35 [0.09, 1.34], 0.1144		1.03 [0.09, 11.75], 0.9814		0.45 [0.14, 1.39], 0.1541	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1495		0.00 [-0.07, 0.07], 0.9813		-0.05 [-0.12, 0.02], 0.1940	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	4/32 (12.5)	5/74 (6.8)	2/36 (5.6)	8/147 (5.4)	6/68 (8.8)
RR [95%-CI]; p-value	0.33 [0.08, 1.39], 0.1295		1.22 [0.25, 5.97], 0.8094		0.62 [0.22, 1.71], 0.3525	
OR [95%-CI]; p-value	0.30 [0.06, 1.43], 0.1126		1.23 [0.23, 6.68], 0.8087		0.59 [0.20, 1.79], 0.3501	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1823		0.01 [-0.08, 0.11], 0.8026		-0.03 [-0.11, 0.04], 0.3878	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_3_m_pt_ae10pct_bl25d.sas using SAS 9.4

Table 12.4.8.1.1.s9
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.7329		0.8770		0.9833	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	1/40 (2.5)	3/70 (4.3)	2/36 (5.6)	6/138 (4.3)	3/76 (3.9)
RR [95%-CI]; p-value	1.76 [0.19, 16.40], 0.6175		0.77 [0.13, 4.41], 0.7705		1.10 [0.28, 4.28], 0.8890	
OR [95%-CI]; p-value	1.80 [0.18, 17.91], 0.6114		0.76 [0.12, 4.77], 0.7702		1.11 [0.27, 4.55], 0.8889	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5856		-0.01 [-0.10, 0.08], 0.7788		0.00 [-0.05, 0.06], 0.8874	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	5/73 (6.8)	2/32 (6.3)	2/74 (2.7)	1/36 (2.8)	7/147 (4.8)	3/68 (4.4)
RR [95%-CI]; p-value	1.10 [0.22, 5.35], 0.9099		0.97 [0.09, 10.38], 0.9819		1.08 [0.29, 4.05], 0.9098	
OR [95%-CI]; p-value	1.10 [0.20, 6.01], 0.9098		0.97 [0.09, 11.09], 0.9819		1.08 [0.27, 4.32], 0.9097	
RD [95%-CI]; p-value	0.01 [-0.10, 0.11], 0.9083		-0.00 [-0.07, 0.06], 0.9820		0.00 [-0.06, 0.06], 0.9085	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_8_1_1_m_soc_sae5pct_bl25d.sas using SAS 9.4

Table 12.4.8.1.2.s9
Summary of SAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_8_1_2_m_pt_sae5pct_bl25d.sas using SAS 9.4

Table 12.4.5.1.1.s9
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_5_1_1_m_soc_aeg35pct_bl25d.sas using SAS 9.4

Table 12.4.5.1.2.s9
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_5_1_2_m_pt_aeg35pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Cardiac disorders						
Interaction p-value	0.1195		0.4984		0.1099	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	6/70 (8.6)	3/36 (8.3)	10/138 (7.2)	10/76 (13.2)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.03 [0.27, 3.87], 0.9668		0.55 [0.24, 1.26], 0.1593	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.03 [0.24, 4.39], 0.9668		0.52 [0.20, 1.30], 0.1551	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.00 [-0.11, 0.11], 0.9666		-0.06 [-0.15, 0.03], 0.1852	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	2/32 (6.3)	5/74 (6.8)	1/36 (2.8)	12/147 (8.2)	3/68 (4.4)
RR [95%-CI]; p-value	1.53 [0.34, 6.98], 0.5799		2.43 [0.29, 20.06], 0.4089		1.85 [0.54, 6.34], 0.3276	
OR [95%-CI]; p-value	1.59 [0.31, 8.12], 0.5737		2.54 [0.29, 22.55], 0.3885		1.93 [0.53, 7.06], 0.3153	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5434		0.04 [-0.04, 0.12], 0.3201		0.04 [-0.03, 0.10], 0.2645	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Interaction p-value	0.6434		0.4204		0.4477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	15/68 (22.1)	11/40 (27.5)	15/70 (21.4)	3/36 (8.3)	30/138 (21.7)	14/76 (18.4)
RR [95%-CI]; p-value	0.80 [0.41, 1.57], 0.5208		2.57 [0.80, 8.31], 0.1144		1.18 [0.67, 2.09], 0.5685	
OR [95%-CI]; p-value	0.75 [0.30, 1.84], 0.5230		3.00 [0.81, 11.15], 0.0890		1.23 [0.61, 2.49], 0.5655	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5302		0.13 [-0.00, 0.26], 0.0516		0.03 [-0.08, 0.14], 0.5581	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	13/73 (17.8)	9/32 (28.1)	11/74 (14.9)	4/36 (11.1)	24/147 (16.3)	13/68 (19.1)
RR [95%-CI]; p-value	0.63 [0.30, 1.33], 0.2270		1.34 [0.46, 3.91], 0.5949		0.85 [0.46, 1.57], 0.6125	
OR [95%-CI]; p-value	0.55 [0.21, 1.47], 0.2318		1.40 [0.41, 4.74], 0.5904		0.83 [0.39, 1.74], 0.6141	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2581		0.04 [-0.09, 0.17], 0.5738		-0.03 [-0.14, 0.08], 0.6219	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
General disorders and administration site conditions						
Interaction p-value	0.1769		0.7513		0.2112	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	9/68 (13.2)	5/40 (12.5)	10/70 (14.3)	6/36 (16.7)	19/138 (13.8)	11/76 (14.5)
RR [95%-CI]; p-value	1.06 [0.38, 2.94], 0.9126		0.86 [0.34, 2.17], 0.7450		0.95 [0.48, 1.89], 0.8867	
OR [95%-CI]; p-value	1.07 [0.33, 3.44], 0.9125		0.83 [0.28, 2.51], 0.7457		0.94 [0.42, 2.10], 0.8869	
RD [95%-CI]; p-value	0.01 [-0.12, 0.14], 0.9120		-0.02 [-0.17, 0.12], 0.7505		-0.01 [-0.10, 0.09], 0.8875	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	10/32 (31.3)	7/74 (9.5)	5/36 (13.9)	17/147 (11.6)	15/68 (22.1)
RR [95%-CI]; p-value	0.44 [0.20, 0.95], 0.0362		0.68 [0.23, 2.00], 0.4843		0.52 [0.28, 0.99], 0.0452	
OR [95%-CI]; p-value	0.35 [0.13, 0.95], 0.0350		0.65 [0.19, 2.20], 0.4844		0.46 [0.22, 0.99], 0.0444	
RD [95%-CI]; p-value	-0.18 [-0.35, 0.00], 0.0545		-0.04 [-0.18, 0.09], 0.5081		-0.10 [-0.22, 0.01], 0.0646	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Interaction p-value	0.1286		0.1763		0.0462	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	23/68 (33.8)	10/40 (25.0)	20/70 (28.6)	7/36 (19.4)	43/138 (31.2)	17/76 (22.4)
RR [95%-CI]; p-value	1.35 [0.72, 2.54], 0.3481		1.47 [0.69, 3.15], 0.3217		1.39 [0.86, 2.27], 0.1820	
OR [95%-CI]; p-value	1.53 [0.64, 3.68], 0.3364		1.66 [0.63, 4.39], 0.3071		1.57 [0.82, 3.01], 0.1707	
RD [95%-CI]; p-value	0.09 [-0.09, 0.26], 0.3233		0.09 [-0.08, 0.26], 0.2843		0.09 [-0.03, 0.21], 0.1560	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	15/73 (20.5)	10/32 (31.3)	13/74 (17.6)	9/36 (25.0)	28/147 (19.0)	19/68 (27.9)
RR [95%-CI]; p-value	0.66 [0.33, 1.30], 0.2295		0.70 [0.33, 1.49], 0.3570		0.68 [0.41, 1.13], 0.1383	
OR [95%-CI]; p-value	0.57 [0.22, 1.45], 0.2359		0.64 [0.24, 1.67], 0.3605		0.61 [0.31, 1.19], 0.1423	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.08], 0.2580		-0.07 [-0.24, 0.09], 0.3799		-0.09 [-0.21, 0.04], 0.1602	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Injury, poisoning and procedural complications						
Interaction p-value	0.2221		0.2372		0.0870	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	4/40 (10.0)	3/70 (4.3)	2/36 (5.6)	10/138 (7.2)	6/76 (7.9)
RR [95%-CI]; p-value	1.03 [0.32, 3.30], 0.9611		0.77 [0.13, 4.41], 0.7705		0.92 [0.35, 2.43], 0.8629	
OR [95%-CI]; p-value	1.03 [0.28, 3.77], 0.9611		0.76 [0.12, 4.77], 0.7702		0.91 [0.32, 2.61], 0.8630	
RD [95%-CI]; p-value	0.00 [-0.11, 0.12], 0.9609		-0.01 [-0.10, 0.08], 0.7788		-0.01 [-0.08, 0.07], 0.8645	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	1/32 (3.1)	8/74 (10.8)	1/36 (2.8)	18/147 (12.2)	2/68 (2.9)
RR [95%-CI]; p-value	4.38 [0.59, 32.82], 0.1502		3.89 [0.51, 29.94], 0.1918		4.16 [0.99, 17.44], 0.0510	
OR [95%-CI]; p-value	4.92 [0.60, 40.19], 0.1034		4.24 [0.51, 35.30], 0.1492		4.60 [1.04, 20.45], 0.0290	
RD [95%-CI]; p-value	0.11 [0.01, 0.21], 0.0368		0.08 [-0.01, 0.17], 0.0763		0.09 [0.03, 0.16], 0.0061	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Investigations						
Interaction p-value	0.5193		0.6986		0.5039	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	7/70 (10.0)	3/36 (8.3)	18/138 (13.0)	9/76 (11.8)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		1.20 [0.33, 4.37], 0.7820		1.10 [0.52, 2.33], 0.8005	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		1.22 [0.30, 5.04], 0.7810		1.12 [0.48, 2.62], 0.8000	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.02 [-0.10, 0.13], 0.7753		0.01 [-0.08, 0.10], 0.7976	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	4/32 (12.5)	7/74 (9.5)	4/36 (11.1)	13/147 (8.8)	8/68 (11.8)
RR [95%-CI]; p-value	0.66 [0.20, 2.17], 0.4917		0.85 [0.27, 2.72], 0.7861		0.75 [0.33, 1.73], 0.5016	
OR [95%-CI]; p-value	0.63 [0.16, 2.39], 0.4915		0.84 [0.23, 3.06], 0.7864		0.73 [0.29, 1.85], 0.5023	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5211		-0.02 [-0.14, 0.11], 0.7914		-0.03 [-0.12, 0.06], 0.5213	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Metabolism and nutrition disorders						
Interaction p-value	0.3592		0.7852		0.3259	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	18/68 (26.5)	17/40 (42.5)	14/70 (20.0)	8/36 (22.2)	32/138 (23.2)	25/76 (32.9)
RR [95%-CI]; p-value	0.62 [0.36, 1.06], 0.0832		0.90 [0.42, 1.94], 0.7886		0.70 [0.45, 1.10], 0.1210	
OR [95%-CI]; p-value	0.49 [0.21, 1.11], 0.0857		0.88 [0.33, 2.33], 0.7893		0.62 [0.33, 1.15], 0.1243	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.03], 0.0906		-0.02 [-0.19, 0.14], 0.7918		-0.10 [-0.22, 0.03], 0.1340	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	10/73 (13.7)	4/32 (12.5)	11/74 (14.9)	5/36 (13.9)	21/147 (14.3)	9/68 (13.2)
RR [95%-CI]; p-value	1.10 [0.37, 3.24], 0.8683		1.07 [0.40, 2.85], 0.8919		1.08 [0.52, 2.23], 0.8367	
OR [95%-CI]; p-value	1.11 [0.32, 3.85], 0.8679		1.08 [0.35, 3.39], 0.8916		1.09 [0.47, 2.53], 0.8362	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8659		0.01 [-0.13, 0.15], 0.8906		0.01 [-0.09, 0.11], 0.8343	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0583		0.3407		0.0358	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	15/40 (37.5)	9/70 (12.9)	8/36 (22.2)	17/138 (12.3)	23/76 (30.3)
RR [95%-CI]; p-value	0.31 [0.15, 0.67], 0.0029		0.58 [0.24, 1.37], 0.2142		0.41 [0.23, 0.71], 0.0017	
OR [95%-CI]; p-value	0.22 [0.08, 0.59], 0.0016		0.52 [0.18, 1.48], 0.2134		0.32 [0.16, 0.66], 0.0013	
RD [95%-CI]; p-value	-0.26 [-0.43, -0.09], 0.0027		-0.09 [-0.25, 0.06], 0.2418		-0.18 [-0.30, -0.06], 0.0026	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	16/73 (21.9)	8/32 (25.0)	13/74 (17.6)	6/36 (16.7)	29/147 (19.7)	14/68 (20.6)
RR [95%-CI]; p-value	0.88 [0.42, 1.84], 0.7275		1.05 [0.44, 2.55], 0.9068		0.96 [0.54, 1.69], 0.8832	
OR [95%-CI]; p-value	0.84 [0.32, 2.23], 0.7292		1.07 [0.37, 3.08], 0.9066		0.95 [0.46, 1.94], 0.8834	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7336		0.01 [-0.14, 0.16], 0.9060		-0.01 [-0.12, 0.11], 0.8841	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Nervous system disorders						
Interaction p-value	0.4751		0.9511		0.8297	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	7/40 (17.5)	12/70 (17.1)	5/36 (13.9)	16/138 (11.6)	12/76 (15.8)
RR [95%-CI]; p-value	0.34 [0.10, 1.08], 0.0666		1.23 [0.47, 3.23], 0.6683		0.73 [0.37, 1.47], 0.3832	
OR [95%-CI]; p-value	0.29 [0.08, 1.08], 0.0539		1.28 [0.41, 3.97], 0.6655		0.70 [0.31, 1.57], 0.3838	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.01], 0.0807		0.03 [-0.11, 0.18], 0.6565		-0.04 [-0.14, 0.06], 0.4007	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	8/73 (11.0)	6/32 (18.8)	8/74 (10.8)	3/36 (8.3)	16/147 (10.9)	9/68 (13.2)
RR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2796		1.30 [0.37, 4.60], 0.6869		0.82 [0.38, 1.77], 0.6161	
OR [95%-CI]; p-value	0.53 [0.17, 1.69], 0.2797		1.33 [0.33, 5.36], 0.6844		0.80 [0.33, 1.92], 0.6170	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.08], 0.3184		0.02 [-0.09, 0.14], 0.6720		-0.02 [-0.12, 0.07], 0.6276	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Renal and urinary disorders						
Interaction p-value	0.4623		0.9095		0.7196	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	6/68 (8.8)	4/40 (10.0)	7/70 (10.0)	4/36 (11.1)	13/138 (9.4)	8/76 (10.5)
RR [95%-CI]; p-value	0.88 [0.26, 2.94], 0.8385		0.90 [0.28, 2.87], 0.8588		0.89 [0.39, 2.06], 0.7944	
OR [95%-CI]; p-value	0.87 [0.23, 3.29], 0.8386		0.89 [0.24, 3.26], 0.8590		0.88 [0.35, 2.24], 0.7947	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.10], 0.8409		-0.01 [-0.14, 0.11], 0.8610		-0.01 [-0.10, 0.07], 0.7975	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	5/73 (6.8)	1/32 (3.1)	5/74 (6.8)	3/36 (8.3)	10/147 (6.8)	4/68 (5.9)
RR [95%-CI]; p-value	2.19 [0.27, 18.01], 0.4653		0.81 [0.21, 3.21], 0.7650		1.16 [0.38, 3.56], 0.7998	
OR [95%-CI]; p-value	2.28 [0.26, 20.34], 0.4492		0.80 [0.18, 3.54], 0.7651		1.17 [0.35, 3.87], 0.7992	
RD [95%-CI]; p-value	0.04 [-0.05, 0.12], 0.3827		-0.02 [-0.12, 0.09], 0.7725		0.01 [-0.06, 0.08], 0.7943	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
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N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.2828		0.2380		0.1477	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	11/68 (16.2)	6/40 (15.0)	9/70 (12.9)	2/36 (5.6)	20/138 (14.5)	8/76 (10.5)
RR [95%-CI]; p-value	1.08 [0.43, 2.69], 0.8715		2.31 [0.53, 10.15], 0.2660		1.38 [0.64, 2.98], 0.4161	
OR [95%-CI]; p-value	1.09 [0.37, 3.23], 0.8712		2.51 [0.51, 12.28], 0.2431		1.44 [0.60, 3.45], 0.4103	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8702		0.07 [-0.04, 0.18], 0.1867		0.04 [-0.05, 0.13], 0.3909	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	6/32 (18.8)	8/74 (10.8)	5/36 (13.9)	15/147 (10.2)	11/68 (16.2)
RR [95%-CI]; p-value	0.51 [0.19, 1.40], 0.1923		0.78 [0.27, 2.21], 0.6381		0.63 [0.31, 1.30], 0.2116	
OR [95%-CI]; p-value	0.46 [0.14, 1.50], 0.1895		0.75 [0.23, 2.49], 0.6389		0.59 [0.25, 1.36], 0.2117	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.06], 0.2349		-0.03 [-0.16, 0.10], 0.6508		-0.06 [-0.16, 0.04], 0.2431	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4122		0.5245		0.3607	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	5/68 (7.4)	4/40 (10.0)	7/70 (10.0)	2/36 (5.6)	12/138 (8.7)	6/76 (7.9)
RR [95%-CI]; p-value	0.74 [0.21, 2.58], 0.6312		1.80 [0.39, 8.22], 0.4483		1.10 [0.43, 2.82], 0.8402	
OR [95%-CI]; p-value	0.71 [0.18, 2.83], 0.6308		1.89 [0.37, 9.60], 0.4369		1.11 [0.40, 3.09], 0.8399	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.09], 0.6425		0.04 [-0.06, 0.15], 0.3961		0.01 [-0.07, 0.08], 0.8379	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	4/73 (5.5)	5/32 (15.6)	8/74 (10.8)	4/36 (11.1)	12/147 (8.2)	9/68 (13.2)
RR [95%-CI]; p-value	0.35 [0.10, 1.22], 0.0997		0.97 [0.31, 3.02], 0.9622		0.62 [0.27, 1.39], 0.2452	
OR [95%-CI]; p-value	0.31 [0.08, 1.25], 0.0874		0.97 [0.27, 3.46], 0.9622		0.58 [0.23, 1.46], 0.2440	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.03], 0.1443		-0.00 [-0.13, 0.12], 0.9623		-0.05 [-0.14, 0.04], 0.2794	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.2.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Interaction p-value	0.7480		0.7289		0.9661	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	8/68 (11.8)	6/40 (15.0)	7/70 (10.0)	4/36 (11.1)	15/138 (10.9)	10/76 (13.2)
RR [95%-CI]; p-value	0.78 [0.29, 2.10], 0.6284		0.90 [0.28, 2.87], 0.8588		0.83 [0.39, 1.75], 0.6174	
OR [95%-CI]; p-value	0.76 [0.24, 2.36], 0.6288		0.89 [0.24, 3.26], 0.8590		0.80 [0.34, 1.89], 0.6180	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.10], 0.6375		-0.01 [-0.14, 0.11], 0.8610		-0.02 [-0.11, 0.07], 0.6261	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	3/32 (9.4)	4/74 (5.4)	3/36 (8.3)	11/147 (7.5)	6/68 (8.8)
RR [95%-CI]; p-value	1.02 [0.28, 3.70], 0.9726		0.65 [0.15, 2.75], 0.5566		0.85 [0.33, 2.20], 0.7345	
OR [95%-CI]; p-value	1.03 [0.25, 4.25], 0.9726		0.63 [0.13, 2.97], 0.5550		0.84 [0.30, 2.36], 0.7348	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9725		-0.03 [-0.13, 0.07], 0.5809		-0.01 [-0.09, 0.07], 0.7417	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_2_m_soc_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.4.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9649		0.7289		0.8279	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	3/68 (4.4)	7/40 (17.5)	4/70 (5.7)	0/36 (0.0)	7/138 (5.1)	7/76 (9.2)
RR [95%-CI]; p-value	0.25 [0.07, 0.92], 0.0370		4.17 [0.23, 76.77], 0.3365		0.55 [0.20, 1.51], 0.2468	
OR [95%-CI]; p-value	0.22 [0.05, 0.90], 0.0234		4.36 [0.22, 84.87], 0.2902		0.53 [0.18, 1.56], 0.2414	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.00], 0.0442		0.04 [-0.02, 0.11], 0.1982		-0.04 [-0.12, 0.03], 0.2770	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	5/32 (15.6)	2/74 (2.7)	0/36 (0.0)	5/147 (3.4)	5/68 (7.4)
RR [95%-CI]; p-value	0.26 [0.07, 1.03], 0.0560		1.97 [0.09, 42.65], 0.6648		0.46 [0.14, 1.54], 0.2102	
OR [95%-CI]; p-value	0.23 [0.05, 1.04], 0.0406		2.00 [0.09, 45.51], 0.6577		0.44 [0.12, 1.59], 0.2007	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0916		0.01 [-0.04, 0.07], 0.6207		-0.04 [-0.11, 0.03], 0.2590	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_4_m_pt_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.4.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.8538		0.9083		0.7206	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	6/40 (15.0)	2/70 (2.9)	1/36 (2.8)	6/138 (4.3)	7/76 (9.2)
RR [95%-CI]; p-value	0.39 [0.12, 1.31], 0.1273		1.03 [0.10, 10.97], 0.9814		0.47 [0.16, 1.35], 0.1627	
OR [95%-CI]; p-value	0.35 [0.09, 1.34], 0.1144		1.03 [0.09, 11.75], 0.9814		0.45 [0.14, 1.39], 0.1541	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1495		0.00 [-0.07, 0.07], 0.9813		-0.05 [-0.12, 0.02], 0.1940	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	4/32 (12.5)	5/74 (6.8)	2/36 (5.6)	8/147 (5.4)	6/68 (8.8)
RR [95%-CI]; p-value	0.33 [0.08, 1.39], 0.1295		1.22 [0.25, 5.97], 0.8094		0.62 [0.22, 1.71], 0.3525	
OR [95%-CI]; p-value	0.30 [0.06, 1.43], 0.1126		1.23 [0.23, 6.68], 0.8087		0.59 [0.20, 1.79], 0.3501	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.04], 0.1823		0.01 [-0.08, 0.11], 0.8026		-0.03 [-0.11, 0.04], 0.3878	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_4_m_pt_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.4.s9
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Vascular disorders						
Hypertension						
Interaction p-value	0.7853		0.6897		0.6912	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	6/68 (8.8)	3/40 (7.5)	6/70 (8.6)	4/36 (11.1)	12/138 (8.7)	7/76 (9.2)
RR [95%-CI]; p-value	1.18 [0.31, 4.45], 0.8107		0.77 [0.23, 2.56], 0.6716		0.94 [0.39, 2.30], 0.8991	
OR [95%-CI]; p-value	1.19 [0.28, 5.06], 0.8101		0.75 [0.20, 2.85], 0.6718		0.94 [0.35, 2.49], 0.8992	
RD [95%-CI]; p-value	0.01 [-0.09, 0.12], 0.8064		-0.03 [-0.15, 0.10], 0.6828		-0.01 [-0.09, 0.08], 0.8999	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	4/73 (5.5)	2/32 (6.3)	2/74 (2.7)	2/36 (5.6)	6/147 (4.1)	4/68 (5.9)
RR [95%-CI]; p-value	0.88 [0.17, 4.55], 0.8755		0.49 [0.07, 3.32], 0.4618		0.69 [0.20, 2.38], 0.5610	
OR [95%-CI]; p-value	0.87 [0.15, 5.01], 0.8756		0.47 [0.06, 3.50], 0.4533		0.68 [0.19, 2.50], 0.5599	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8785		-0.03 [-0.11, 0.05], 0.5028		-0.02 [-0.08, 0.05], 0.5838	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_4_m_pt_ae1pct_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.4486		0.3000		0.8761	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	7/68 (10.3)	2/40 (5.0)	6/70 (8.6)	3/36 (8.3)	13/138 (9.4)	5/76 (6.6)
RR [95%-CI]; p-value	2.06 [0.45, 9.43], 0.3525		1.03 [0.27, 3.87], 0.9668		1.43 [0.53, 3.86], 0.4784	
OR [95%-CI]; p-value	2.18 [0.43, 11.05], 0.3364		1.03 [0.24, 4.39], 0.9668		1.48 [0.51, 4.31], 0.4736	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.2940		0.00 [-0.11, 0.11], 0.9666		0.03 [-0.05, 0.10], 0.4520	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	8/73 (11.0)	0/32 (0.0)	3/74 (4.1)	4/36 (11.1)	11/147 (7.5)	4/68 (5.9)
RR [95%-CI]; p-value	7.12 [0.42, 120.35], 0.1735		0.36 [0.09, 1.54], 0.1709		1.27 [0.42, 3.85], 0.6702	
OR [95%-CI]; p-value	7.88 [0.44, 141.49], 0.1007		0.34 [0.07, 1.60], 0.1548		1.29 [0.40, 4.22], 0.6683	
RD [95%-CI]; p-value	0.09 [0.01, 0.18], 0.0265		-0.07 [-0.18, 0.04], 0.2171		0.02 [-0.05, 0.09], 0.6552	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9048		0.9841		0.9369	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	1/68 (1.5)	0/40 (0.0)	1/70 (1.4)	1/36 (2.8)	2/138 (1.4)	1/76 (1.3)
RR [95%-CI]; p-value	1.19 [0.04, 34.72], 0.9190		0.51 [0.03, 7.98], 0.6346		1.10 [0.10, 11.95], 0.9367	
OR [95%-CI]; p-value	1.19 [0.04, 36.40], 0.9189		0.51 [0.03, 8.35], 0.6287		1.10 [0.10, 12.37], 0.9366	
RD [95%-CI]; p-value	0.00 [-0.04, 0.05], 0.9171		-0.01 [-0.07, 0.05], 0.6618		0.00 [-0.03, 0.03], 0.9358	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	1/73 (1.4)	0/32 (0.0)	0/74 (0.0)	0/36 (0.0)	1/147 (0.7)	0/68 (0.0)
RR [95%-CI]; p-value	0.89 [0.03, 25.88], 0.9462		NA		0.93 [0.03, 27.44], 0.9674	
OR [95%-CI]; p-value	0.89 [0.03, 27.18], 0.9462		NA		0.93 [0.03, 28.11], 0.9674	
RD [95%-CI]; p-value	-0.00 [-0.05, 0.05], 0.9473		NA		-0.00 [-0.02, 0.02], 0.9678	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4447		0.2502		0.7378	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	6/68 (8.8)	2/40 (5.0)	5/70 (7.1)	2/36 (5.6)	11/138 (8.0)	4/76 (5.3)
RR [95%-CI]; p-value	1.76 [0.37, 8.33], 0.4732		1.29 [0.26, 6.30], 0.7567		1.51 [0.50, 4.59], 0.4634	
OR [95%-CI]; p-value	1.84 [0.35, 9.58], 0.4638		1.31 [0.24, 7.10], 0.7553		1.56 [0.48, 5.08], 0.4578	
RD [95%-CI]; p-value	0.04 [-0.06, 0.13], 0.4323		0.02 [-0.08, 0.11], 0.7462		0.03 [-0.04, 0.09], 0.4320	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	0/32 (0.0)	3/74 (4.1)	4/36 (11.1)	10/147 (6.8)	4/68 (5.9)
RR [95%-CI]; p-value	6.23 [0.36, 106.59], 0.2065		0.36 [0.09, 1.54], 0.1709		1.16 [0.38, 3.56], 0.7998	
OR [95%-CI]; p-value	6.79 [0.37, 123.36], 0.1374		0.34 [0.07, 1.60], 0.1548		1.17 [0.35, 3.87], 0.7992	
RD [95%-CI]; p-value	0.08 [0.00, 0.16], 0.0477		-0.07 [-0.18, 0.04], 0.2171		0.01 [-0.06, 0.08], 0.7943	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.4840		0.7477		0.6121	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	2/68 (2.9)	1/40 (2.5)	2/70 (2.9)	0/36 (0.0)	4/138 (2.9)	1/76 (1.3)
RR [95%-CI]; p-value	1.18 [0.11, 12.57], 0.8930		2.09 [0.10, 45.07], 0.6392		2.20 [0.25, 19.36], 0.4763	
OR [95%-CI]; p-value	1.18 [0.10, 13.46], 0.8928		2.12 [0.09, 48.21], 0.6304		2.24 [0.25, 20.40], 0.4632	
RD [95%-CI]; p-value	0.00 [-0.06, 0.07], 0.8906		0.01 [-0.04, 0.07], 0.5912		0.02 [-0.02, 0.05], 0.4136	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	5/73 (6.8)	0/32 (0.0)	1/74 (1.4)	0/36 (0.0)	6/147 (4.1)	0/68 (0.0)
RR [95%-CI]; p-value	4.45 [0.25, 79.12], 0.3091		0.99 [0.03, 28.73], 0.9937		5.59 [0.32, 98.69], 0.2399	
OR [95%-CI]; p-value	4.71 [0.25, 88.78], 0.2572		0.99 [0.03, 30.09], 0.9937		5.79 [0.32, 105.12], 0.1804	
RD [95%-CI]; p-value	0.05 [-0.02, 0.12], 0.1468		-0.00 [-0.05, 0.05], 0.9937		0.03 [-0.00, 0.07], 0.0823	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7524		0.3726		0.6508	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	5/68 (7.4)	5/40 (12.5)	9/70 (12.9)	3/36 (8.3)	14/138 (10.1)	8/76 (10.5)
RR [95%-CI]; p-value	0.59 [0.18, 1.91], 0.3767		1.54 [0.45, 5.35], 0.4942		0.96 [0.42, 2.19], 0.9299	
OR [95%-CI]; p-value	0.56 [0.15, 2.05], 0.3729		1.62 [0.41, 6.41], 0.4863		0.96 [0.38, 2.40], 0.9299	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.07], 0.3998		0.05 [-0.07, 0.16], 0.4584		-0.00 [-0.09, 0.08], 0.9303	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	7/73 (9.6)	4/32 (12.5)	4/74 (5.4)	3/36 (8.3)	11/147 (7.5)	7/68 (10.3)
RR [95%-CI]; p-value	0.77 [0.24, 2.44], 0.6531		0.65 [0.15, 2.75], 0.5566		0.73 [0.29, 1.79], 0.4888	
OR [95%-CI]; p-value	0.74 [0.20, 2.74], 0.6539		0.63 [0.13, 2.97], 0.5550		0.70 [0.26, 1.91], 0.4889	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.10], 0.6680		-0.03 [-0.13, 0.07], 0.5809		-0.03 [-0.11, 0.06], 0.5110	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9048		0.3667		0.4157	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	1/68 (1.5)	0/40 (0.0)	3/70 (4.3)	0/36 (0.0)	4/138 (2.9)	0/76 (0.0)
RR [95%-CI]; p-value	1.19 [0.04, 34.72], 0.9190		3.13 [0.16, 60.80], 0.4512		4.43 [0.24, 82.77], 0.3185	
OR [95%-CI]; p-value	1.19 [0.04, 36.40], 0.9189		3.22 [0.16, 66.14], 0.4231		4.54 [0.24, 86.98], 0.2718	
RD [95%-CI]; p-value	0.00 [-0.04, 0.05], 0.9171		0.03 [-0.03, 0.09], 0.3457		0.02 [-0.01, 0.06], 0.1865	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	1/73 (1.4)	0/32 (0.0)	1/74 (1.4)	1/36 (2.8)	2/147 (1.4)	1/68 (1.5)
RR [95%-CI]; p-value	0.89 [0.03, 25.88], 0.9462		0.49 [0.03, 7.56], 0.6067		0.93 [0.09, 10.03], 0.9490	
OR [95%-CI]; p-value	0.89 [0.03, 27.18], 0.9462		0.48 [0.03, 7.89], 0.5993		0.92 [0.08, 10.37], 0.9490	
RD [95%-CI]; p-value	-0.00 [-0.05, 0.05], 0.9473		-0.01 [-0.07, 0.05], 0.6400		-0.00 [-0.04, 0.03], 0.9497	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7052		0.3804		0.7120	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	4/68 (5.9)	5/40 (12.5)	7/70 (10.0)	3/36 (8.3)	11/138 (8.0)	8/76 (10.5)
RR [95%-CI]; p-value	0.47 [0.13, 1.65], 0.2393		1.20 [0.33, 4.37], 0.7820		0.76 [0.32, 1.80], 0.5294	
OR [95%-CI]; p-value	0.44 [0.11, 1.74], 0.2295		1.22 [0.30, 5.04], 0.7810		0.74 [0.28, 1.92], 0.5294	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.05], 0.2666		0.02 [-0.10, 0.13], 0.7753		-0.03 [-0.11, 0.06], 0.5437	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	6/73 (8.2)	4/32 (12.5)	3/74 (4.1)	3/36 (8.3)	9/147 (6.1)	7/68 (10.3)
RR [95%-CI]; p-value	0.66 [0.20, 2.17], 0.4917		0.49 [0.10, 2.29], 0.3622		0.59 [0.23, 1.53], 0.2812	
OR [95%-CI]; p-value	0.63 [0.16, 2.39], 0.4915		0.46 [0.09, 2.43], 0.3537		0.57 [0.20, 1.60], 0.2784	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5211		-0.04 [-0.14, 0.06], 0.4056		-0.04 [-0.12, 0.04], 0.3185	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.7.s9
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9581		0.5464		0.6334	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	2/68 (2.9)	0/40 (0.0)	3/70 (4.3)	0/36 (0.0)	5/138 (3.6)	0/76 (0.0)
RR [95%-CI]; p-value	2.38 [0.11, 51.55], 0.5800		3.13 [0.16, 60.80], 0.4512		5.54 [0.31, 100.11], 0.2460	
OR [95%-CI]; p-value	2.42 [0.11, 55.11], 0.5666		3.22 [0.16, 66.14], 0.4231		5.71 [0.31, 106.03], 0.1875	
RD [95%-CI]; p-value	0.02 [-0.04, 0.07], 0.5250		0.03 [-0.03, 0.09], 0.3457		0.03 [-0.01, 0.07], 0.1062	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	3/73 (4.1)	0/32 (0.0)	2/74 (2.7)	1/36 (2.8)	5/147 (3.4)	1/68 (1.5)
RR [95%-CI]; p-value	2.67 [0.14, 51.82], 0.5161		0.97 [0.09, 10.38], 0.9819		2.31 [0.28, 19.42], 0.4399	
OR [95%-CI]; p-value	2.74 [0.13, 56.37], 0.4960		0.97 [0.09, 11.09], 0.9819		2.36 [0.27, 20.59], 0.4241	
RD [95%-CI]; p-value	0.03 [-0.04, 0.09], 0.4176		-0.00 [-0.07, 0.06], 0.9820		0.02 [-0.02, 0.06], 0.3555	

Abbreviations: CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_7_m_pt_smq_bl25d.sas using SAS 9.4

Table 12.4.4.1.6.s9
Overall Summary of Adverse Drug Reactions (ADR)
ITT Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=141)	Placebo (N=72)	ER-Calcifediol (N=144)	Placebo (N=72)	ER-Calcifediol (N=285)	Placebo (N=144)
Number of Patients with Any ADR						
Interaction p-value	0.5939		0.5609		0.3402	
1.Baseline 25D < 20 ng/mL	N1=68	N1=40	N1=70	N1=36	N1=138	N1=76
n/N1 (%)	12/68 (17.6)	9/40 (22.5)	18/70 (25.7)	5/36 (13.9)	30/138 (21.7)	14/76 (18.4)
RR [95%-CI]; p-value	0.78 [0.36, 1.70], 0.5368		1.85 [0.75, 4.58], 0.1825		1.18 [0.67, 2.09], 0.5685	
OR [95%-CI]; p-value	0.74 [0.28, 1.95], 0.5383		2.15 [0.72, 6.36], 0.1619		1.23 [0.61, 2.49], 0.5655	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5471		0.12 [-0.03, 0.27], 0.1285		0.03 [-0.08, 0.14], 0.5581	
2.Baseline 25D≥ 20 ng/mL	N2=73	N2=32	N2=74	N2=36	N2=147	N2=68
n/N2 (%)	12/73 (16.4)	9/32 (28.1)	10/74 (13.5)	4/36 (11.1)	22/147 (15.0)	13/68 (19.1)
RR [95%-CI]; p-value	0.58 [0.27, 1.25], 0.1648		1.22 [0.41, 3.61], 0.7246		0.78 [0.42, 1.46], 0.4408	
OR [95%-CI]; p-value	0.50 [0.19, 1.35], 0.1682		1.25 [0.36, 4.30], 0.7228		0.74 [0.35, 1.58], 0.4432	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1968		0.02 [-0.10, 0.15], 0.7148		-0.04 [-0.15, 0.07], 0.4587	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; ITT: Intention-To-Treat; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d/T12_4_4_1_6_m_pt_adr_bl25d.sas using SAS 9.4

Nachberechnungsdokument

Subgruppenanalysen zu den Sicherheitsendpunkten (Unerwünschte Ereignisse (PP-Population))

Folgende Daten werden für die PP-Population:

- Gesamtraten
  - Jegliche UE
  - SUE
  - UE, die zum Therapieabbruch führten
  - UE, die zum Studienabbruch führten
  - UE, die zum Tod führten
  - UE nach Schweregrad (mild, moderat, schwer)
- Detailanalysen
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens 10 % der Patienten in einem Behandlungsarm aufgetreten sind
  - SUE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - Schwere UE nach SOC und PT, die bei mindestens 5 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE (unabhängig vom Schweregrad) nach SOC und PT, die bei mindestens zehn Patienten und bei mindestens 1 % der Patienten in einem Behandlungsarm aufgetreten sind
  - UE von besonderem Interesse (akutes Nierenversagen, Herzerkrankung
  - UE ohne erkrankungsbezogene Ereignisse
  - UE nach SOC und PT, die zum Abbruch führten

für folgende Subgruppen dargestellt:

- Alter
- Geschlecht
- Gewicht
- Abstammung
- CKD-Stadium zu Baseline
- Schwere des sHPT zu Baseline
- Dosierung
- Einnahme von Vitamin D-Supplementen zu Baseline
- 25(OH)D-Spiegel im Serum zu Baseline

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.7432		0.8365		0.6389	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	37/51 (72.5)	22/28 (78.6)	25/40 (62.5)	16/26 (61.5)	62/91 (68.1)	38/54 (70.4)
RR [95%-CI]; p-value	0.92 [0.71, 1.19], 0.5427		1.02 [0.69, 1.50], 0.9375		0.97 [0.77, 1.21], 0.7762	
OR [95%-CI]; p-value	0.72 [0.24, 2.15], 0.5560		1.04 [0.38, 2.88], 0.9373		0.90 [0.43, 1.87], 0.7782	
RD [95%-CI]; p-value	-0.06 [-0.26, 0.13], 0.5454		0.01 [-0.23, 0.25], 0.9373		-0.02 [-0.18, 0.13], 0.7770	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	46/64 (71.9)	28/34 (82.4)	47/79 (59.5)	21/34 (61.8)	93/143 (65.0)	49/68 (72.1)
RR [95%-CI]; p-value	0.87 [0.70, 1.09], 0.2220		0.96 [0.70, 1.33], 0.8191		0.90 [0.75, 1.09], 0.2917	
OR [95%-CI]; p-value	0.55 [0.19, 1.54], 0.2509		0.91 [0.40, 2.07], 0.8211		0.72 [0.38, 1.36], 0.3094	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.06], 0.2242		-0.02 [-0.22, 0.17], 0.8203		-0.07 [-0.20, 0.06], 0.2978	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.5055		0.8620		0.6871	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	6/28 (21.4)	6/40 (15.0)	1/26 (3.8)	12/91 (13.2)	7/54 (13.0)
RR [95%-CI]; p-value	0.55 [0.20, 1.54], 0.2554		3.90 [0.50, 30.56], 0.1951		1.02 [0.43, 2.43], 0.9692	
OR [95%-CI]; p-value	0.49 [0.14, 1.69], 0.2523		4.41 [0.50, 38.99], 0.1505		1.02 [0.38, 2.77], 0.9692	
RD [95%-CI]; p-value	-0.10 [-0.27, 0.08], 0.2814		0.11 [-0.02, 0.24], 0.1004		0.00 [-0.11, 0.12], 0.9691	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	4/34 (11.8)	7/79 (8.9)	1/34 (2.9)	14/143 (9.8)	5/68 (7.4)
RR [95%-CI]; p-value	0.93 [0.29, 2.95], 0.9016		3.01 [0.39, 23.55], 0.2932		1.33 [0.50, 3.55], 0.5667	
OR [95%-CI]; p-value	0.92 [0.25, 3.40], 0.9017		3.21 [0.38, 27.14], 0.2605		1.37 [0.47, 3.97], 0.5633	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.9027		0.06 [-0.03, 0.14], 0.1701		0.02 [-0.05, 0.10], 0.5447	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.3659		0.3114		0.2517	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	4/51 (7.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	6/91 (6.6)	2/54 (3.7)
RR [95%-CI]; p-value	4.47 [0.25, 81.57], 0.3122		0.65 [0.10, 4.33], 0.6562		1.78 [0.37, 8.51], 0.4700	
OR [95%-CI]; p-value	4.77 [0.24, 93.55], 0.2599		0.63 [0.08, 4.79], 0.6542		1.84 [0.36, 9.43], 0.4612	
RD [95%-CI]; p-value	0.06 [-0.03, 0.15], 0.1757		-0.03 [-0.15, 0.10], 0.6671		0.03 [-0.04, 0.10], 0.4294	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	8/64 (12.5)	4/34 (11.8)	1/79 (1.3)	3/34 (8.8)	9/143 (6.3)	7/68 (10.3)
RR [95%-CI]; p-value	1.06 [0.34, 3.28], 0.9159		0.14 [0.02, 1.33], 0.0875		0.61 [0.24, 1.57], 0.3073	
OR [95%-CI]; p-value	1.07 [0.30, 3.85], 0.9158		0.13 [0.01, 1.32], 0.0461		0.59 [0.21, 1.64], 0.3050	
RD [95%-CI]; p-value	0.01 [-0.13, 0.14], 0.9151		-0.08 [-0.17, 0.02], 0.1325		-0.04 [-0.12, 0.04], 0.3417	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.2364		0.8151		0.4394	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	8/51 (15.7)	2/28 (7.1)	5/40 (12.5)	4/26 (15.4)	13/91 (14.3)	6/54 (11.1)
RR [95%-CI]; p-value	2.20 [0.50, 9.64], 0.2973		0.81 [0.24, 2.75], 0.7384		1.29 [0.52, 3.18], 0.5870	
OR [95%-CI]; p-value	2.42 [0.48, 12.27], 0.2747		0.79 [0.19, 3.25], 0.7386		1.33 [0.48, 3.74], 0.5839	
RD [95%-CI]; p-value	0.09 [-0.05, 0.22], 0.2252		-0.03 [-0.20, 0.14], 0.7430		0.03 [-0.08, 0.14], 0.5731	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	12/64 (18.8)	8/34 (23.5)	7/79 (8.9)	3/34 (8.8)	19/143 (13.3)	11/68 (16.2)
RR [95%-CI]; p-value	0.80 [0.36, 1.76], 0.5742		1.00 [0.28, 3.65], 0.9949		0.82 [0.41, 1.63], 0.5729	
OR [95%-CI]; p-value	0.75 [0.27, 2.06], 0.5763		1.00 [0.24, 4.14], 0.9949		0.79 [0.35, 1.78], 0.5743	
RD [95%-CI]; p-value	-0.05 [-0.22, 0.12], 0.5853		0.00 [-0.11, 0.11], 0.9949		-0.03 [-0.13, 0.07], 0.5850	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.7955		0.9959		0.9386	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	2/51 (3.9)	1/28 (3.6)	2/40 (5.0)	0/26 (0.0)	4/91 (4.4)	1/54 (1.9)
RR [95%-CI]; p-value	1.10 [0.10, 11.58], 0.9380		2.65 [0.12, 56.51], 0.5325		2.37 [0.27, 20.69], 0.4340	
OR [95%-CI]; p-value	1.10 [0.10, 12.72], 0.9379		2.74 [0.12, 63.16], 0.5135		2.44 [0.27, 22.39], 0.4170	
RD [95%-CI]; p-value	0.00 [-0.08, 0.09], 0.9371		0.03 [-0.05, 0.12], 0.4735		0.03 [-0.03, 0.08], 0.3680	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	2/34 (5.9)	3/79 (3.8)	0/34 (0.0)	9/143 (6.3)	2/68 (2.9)
RR [95%-CI]; p-value	1.59 [0.34, 7.47], 0.5544		2.62 [0.13, 50.92], 0.5246		2.14 [0.48, 9.64], 0.3217	
OR [95%-CI]; p-value	1.66 [0.32, 8.68], 0.5478		2.68 [0.13, 55.06], 0.5057		2.22 [0.47, 10.55], 0.3059	
RD [95%-CI]; p-value	0.03 [-0.07, 0.14], 0.5206		0.02 [-0.03, 0.08], 0.4277		0.03 [-0.02, 0.09], 0.2452	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9866		NA		0.9264	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	0/40 (0.0)	0/26 (0.0)	0/91 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	1/34 (2.9)	0/79 (0.0)	0/34 (0.0)	1/143 (0.7)	1/68 (1.5)
RR [95%-CI]; p-value	0.53 [0.03, 8.23], 0.6510		NA		0.48 [0.03, 7.49], 0.5972	
OR [95%-CI]; p-value	0.52 [0.03, 8.65], 0.6459		NA		0.47 [0.03, 7.66], 0.5889	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.6748		NA		-0.01 [-0.04, 0.02], 0.6335	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7777		NA		0.7266	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	0/40 (0.0)	0/26 (0.0)	0/91 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	0/64 (0.0)	1/34 (2.9)	0/79 (0.0)	0/34 (0.0)	0/143 (0.0)	1/68 (1.5)
RR [95%-CI]; p-value	0.26 [0.01, 7.66], 0.4379		NA		0.24 [0.01, 6.98], 0.4041	
OR [95%-CI]; p-value	0.26 [0.01, 7.89], 0.4040		NA		0.23 [0.01, 7.07], 0.3637	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.04], 0.4843		NA		-0.01 [-0.04, 0.02], 0.4663	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.4482		0.9978		0.5496	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	31/51 (60.8)	19/28 (67.9)	21/40 (52.5)	13/26 (50.0)	52/91 (57.1)	32/54 (59.3)
RR [95%-CI]; p-value	0.90 [0.64, 1.25], 0.5221		1.05 [0.65, 1.70], 0.8435		0.96 [0.73, 1.28], 0.8017	
OR [95%-CI]; p-value	0.73 [0.28, 1.94], 0.5327		1.11 [0.41, 2.97], 0.8426		0.92 [0.46, 1.82], 0.8029	
RD [95%-CI]; p-value	-0.07 [-0.29, 0.15], 0.5264		0.03 [-0.22, 0.27], 0.8426		-0.02 [-0.19, 0.14], 0.8025	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	37/64 (57.8)	26/34 (76.5)	39/79 (49.4)	16/34 (47.1)	76/143 (53.1)	42/68 (61.8)
RR [95%-CI]; p-value	0.76 [0.57, 1.00], 0.0505		1.05 [0.69, 1.60], 0.8235		0.86 [0.68, 1.10], 0.2239	
OR [95%-CI]; p-value	0.42 [0.17, 1.07], 0.0665		1.10 [0.49, 2.45], 0.8219		0.70 [0.39, 1.27], 0.2387	
RD [95%-CI]; p-value	-0.19 [-0.37, 0.00], 0.0505		0.02 [-0.18, 0.22], 0.8217		-0.09 [-0.23, 0.06], 0.2327	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.3057		0.5233		0.8247	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	14/51 (27.5)	12/28 (42.9)	15/40 (37.5)	7/26 (26.9)	29/91 (31.9)	19/54 (35.2)
RR [95%-CI]; p-value	0.64 [0.35, 1.19], 0.1578		1.39 [0.66, 2.95], 0.3859		0.91 [0.57, 1.45], 0.6799	
OR [95%-CI]; p-value	0.50 [0.19, 1.33], 0.1633		1.63 [0.55, 4.78], 0.3731		0.86 [0.42, 1.76], 0.6816	
RD [95%-CI]; p-value	-0.15 [-0.37, 0.07], 0.1708		0.11 [-0.12, 0.33], 0.3613		-0.03 [-0.19, 0.13], 0.6833	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	24/64 (37.5)	13/34 (38.2)	21/79 (26.6)	9/34 (26.5)	45/143 (31.5)	22/68 (32.4)
RR [95%-CI]; p-value	0.98 [0.58, 1.67], 0.9429		1.00 [0.51, 1.96], 0.9902		0.97 [0.64, 1.48], 0.8972	
OR [95%-CI]; p-value	0.97 [0.41, 2.28], 0.9430		1.01 [0.40, 2.50], 0.9902		0.96 [0.52, 1.78], 0.8974	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9431		0.00 [-0.18, 0.18], 0.9902		-0.01 [-0.14, 0.13], 0.8976	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.3.1.s1.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.3659		0.3114		0.2517	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	4/51 (7.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	6/91 (6.6)	2/54 (3.7)
RR [95%-CI]; p-value	4.47 [0.25, 81.57], 0.3122		0.65 [0.10, 4.33], 0.6562		1.78 [0.37, 8.51], 0.4700	
OR [95%-CI]; p-value	4.77 [0.24, 93.55], 0.2599		0.63 [0.08, 4.79], 0.6542		1.84 [0.36, 9.43], 0.4612	
RD [95%-CI]; p-value	0.06 [-0.03, 0.15], 0.1757		-0.03 [-0.15, 0.10], 0.6671		0.03 [-0.04, 0.10], 0.4294	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	8/64 (12.5)	4/34 (11.8)	1/79 (1.3)	3/34 (8.8)	9/143 (6.3)	7/68 (10.3)
RR [95%-CI]; p-value	1.06 [0.34, 3.28], 0.9159		0.14 [0.02, 1.33], 0.0875		0.61 [0.24, 1.57], 0.3073	
OR [95%-CI]; p-value	1.07 [0.30, 3.85], 0.9158		0.13 [0.01, 1.32], 0.0461		0.59 [0.21, 1.64], 0.3050	
RD [95%-CI]; p-value	0.01 [-0.13, 0.14], 0.9151		-0.08 [-0.17, 0.02], 0.1325		-0.04 [-0.12, 0.04], 0.3417	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_3_1_m_sf_ttl_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.0833		0.9891		0.1492	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	2/28 (7.1)	1/40 (2.5)	0/26 (0.0)	6/91 (6.6)	2/54 (3.7)
RR [95%-CI]; p-value	1.37 [0.28, 6.62], 0.6933		1.33 [0.05, 38.11], 0.8696		1.78 [0.37, 8.51], 0.4700	
OR [95%-CI]; p-value	1.41 [0.26, 7.80], 0.6905		1.33 [0.04, 41.20], 0.8690		1.84 [0.36, 9.43], 0.4612	
RD [95%-CI]; p-value	0.03 [-0.10, 0.15], 0.6778		0.01 [-0.06, 0.08], 0.8654		0.03 [-0.04, 0.10], 0.4294	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	7/34 (20.6)	6/79 (7.6)	2/34 (5.9)	9/143 (6.3)	9/68 (13.2)
RR [95%-CI]; p-value	0.23 [0.06, 0.82], 0.0242		1.29 [0.27, 6.08], 0.7465		0.48 [0.20, 1.14], 0.0969	
OR [95%-CI]; p-value	0.19 [0.05, 0.79], 0.0133		1.32 [0.25, 6.87], 0.7448		0.44 [0.17, 1.17], 0.0916	
RD [95%-CI]; p-value	-0.16 [-0.30, -0.01], 0.0321		0.02 [-0.08, 0.12], 0.7328		-0.07 [-0.16, 0.02], 0.1299	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.1383		0.1955		0.1489	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	9/28 (32.1)	10/40 (25.0)	5/26 (19.2)	16/91 (17.6)	14/54 (25.9)
RR [95%-CI]; p-value	0.37 [0.15, 0.92], 0.0331		1.30 [0.50, 3.37], 0.5896		0.68 [0.36, 1.28], 0.2295	
OR [95%-CI]; p-value	0.28 [0.09, 0.90], 0.0272		1.40 [0.42, 4.69], 0.5847		0.61 [0.27, 1.37], 0.2305	
RD [95%-CI]; p-value	-0.20 [-0.40, -0.01], 0.0398		0.06 [-0.14, 0.26], 0.5763		-0.08 [-0.22, 0.06], 0.2449	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	15/64 (23.4)	9/34 (26.5)	13/79 (16.5)	1/34 (2.9)	28/143 (19.6)	10/68 (14.7)
RR [95%-CI]; p-value	0.89 [0.43, 1.81], 0.7384		5.59 [0.76, 41.09], 0.0905		1.33 [0.69, 2.58], 0.3965	
OR [95%-CI]; p-value	0.85 [0.33, 2.21], 0.7396		6.50 [0.81, 51.84], 0.0455		1.41 [0.64, 3.11], 0.3892	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7426		0.14 [0.04, 0.23], 0.0078		0.05 [-0.06, 0.16], 0.3691	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.6494		0.8121		0.9156	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	8/51 (15.7)	7/28 (25.0)	4/40 (10.0)	3/26 (11.5)	12/91 (13.2)	10/54 (18.5)
RR [95%-CI]; p-value	0.63 [0.25, 1.55], 0.3120		0.87 [0.21, 3.56], 0.8427		0.71 [0.33, 1.54], 0.3866	
OR [95%-CI]; p-value	0.56 [0.18, 1.75], 0.3127		0.85 [0.17, 4.16], 0.8428		0.67 [0.27, 1.67], 0.3869	
RD [95%-CI]; p-value	-0.09 [-0.28, 0.10], 0.3339		-0.02 [-0.17, 0.14], 0.8448		-0.05 [-0.18, 0.07], 0.4023	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	8/34 (23.5)	10/79 (12.7)	4/34 (11.8)	17/143 (11.9)	12/68 (17.6)
RR [95%-CI]; p-value	0.46 [0.18, 1.17], 0.1046		1.08 [0.36, 3.19], 0.8950		0.67 [0.34, 1.33], 0.2550	
OR [95%-CI]; p-value	0.40 [0.13, 1.22], 0.0994		1.09 [0.32, 3.74], 0.8948		0.63 [0.28, 1.41], 0.2562	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1272		0.01 [-0.12, 0.14], 0.8935		-0.06 [-0.16, 0.05], 0.2824	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1524		0.8272		0.3768	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	14/51 (27.5)	11/28 (39.3)	12/40 (30.0)	7/26 (26.9)	26/91 (28.6)	18/54 (33.3)
RR [95%-CI]; p-value	0.70 [0.37, 1.33], 0.2732		1.11 [0.51, 2.46], 0.7885		0.86 [0.52, 1.41], 0.5439	
OR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2793		1.16 [0.39, 3.49], 0.7873		0.80 [0.39, 1.65], 0.5465	
RD [95%-CI]; p-value	-0.12 [-0.34, 0.10], 0.2883		0.03 [-0.19, 0.25], 0.7858		-0.05 [-0.20, 0.11], 0.5504	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	17/64 (26.6)	6/34 (17.6)	16/79 (20.3)	7/34 (20.6)	33/143 (23.1)	13/68 (19.1)
RR [95%-CI]; p-value	1.51 [0.65, 3.46], 0.3357		0.98 [0.45, 2.17], 0.9676		1.21 [0.68, 2.14], 0.5198	
OR [95%-CI]; p-value	1.69 [0.60, 4.78], 0.3216		0.98 [0.36, 2.65], 0.9676		1.27 [0.62, 2.60], 0.5151	
RD [95%-CI]; p-value	0.09 [-0.08, 0.26], 0.2975		-0.00 [-0.17, 0.16], 0.9677		0.04 [-0.08, 0.16], 0.5043	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0350		0.8073		0.0715	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	10/51 (19.6)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	14/91 (15.4)	5/54 (9.3)
RR [95%-CI]; p-value	1.83 [0.55, 6.11], 0.3256		1.30 [0.26, 6.60], 0.7515		1.66 [0.63, 4.36], 0.3019	
OR [95%-CI]; p-value	2.03 [0.51, 8.10], 0.3078		1.33 [0.23, 7.86], 0.7500		1.78 [0.60, 5.26], 0.2906	
RD [95%-CI]; p-value	0.09 [-0.07, 0.25], 0.2703		0.02 [-0.12, 0.16], 0.7437		0.06 [-0.05, 0.17], 0.2623	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	7/34 (20.6)	7/79 (8.9)	3/34 (8.8)	11/143 (7.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.30 [0.10, 0.96], 0.0432		1.00 [0.28, 3.65], 0.9949		0.52 [0.23, 1.17], 0.1152	
OR [95%-CI]; p-value	0.26 [0.07, 0.95], 0.0323		1.00 [0.24, 4.14], 0.9949		0.48 [0.19, 1.20], 0.1117	
RD [95%-CI]; p-value	-0.14 [-0.29, 0.00], 0.0581		0.00 [-0.11, 0.11], 0.9949		-0.07 [-0.16, 0.02], 0.1472	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8148		0.2299		0.2921	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	9/51 (17.6)	7/28 (25.0)	9/40 (22.5)	4/26 (15.4)	18/91 (19.8)	11/54 (20.4)
RR [95%-CI]; p-value	0.71 [0.29, 1.69], 0.4345		1.46 [0.50, 4.26], 0.4859		0.97 [0.50, 1.90], 0.9315	
OR [95%-CI]; p-value	0.64 [0.21, 1.97], 0.4366		1.60 [0.44, 5.85], 0.4776		0.96 [0.42, 2.23], 0.9316	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.12], 0.4517		0.07 [-0.12, 0.26], 0.4622		-0.01 [-0.14, 0.13], 0.9317	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	12/79 (15.2)	8/34 (23.5)	26/143 (18.2)	20/68 (29.4)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.65 [0.29, 1.44], 0.2832		0.62 [0.37, 1.03], 0.0627	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.58 [0.21, 1.59], 0.2867		0.53 [0.27, 1.05], 0.0648	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.08 [-0.25, 0.08], 0.3162		-0.11 [-0.24, 0.01], 0.0792	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4870		0.8860		0.5472	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	8/28 (28.6)	5/40 (12.5)	5/26 (19.2)	11/91 (12.1)	13/54 (24.1)
RR [95%-CI]; p-value	0.41 [0.16, 1.07], 0.0680		0.65 [0.21, 2.03], 0.4577		0.50 [0.24, 1.04], 0.0640	
OR [95%-CI]; p-value	0.33 [0.10, 1.09], 0.0613		0.60 [0.16, 2.32], 0.4562		0.43 [0.18, 1.05], 0.0604	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0818		-0.07 [-0.25, 0.12], 0.4707		-0.12 [-0.25, 0.01], 0.0757	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	15/79 (19.0)	9/34 (26.5)	29/143 (20.3)	21/68 (30.9)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.72 [0.35, 1.48], 0.3671		0.66 [0.41, 1.06], 0.0870	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.65 [0.25, 1.68], 0.3724		0.57 [0.30, 1.10], 0.0905	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.07 [-0.25, 0.10], 0.3929		-0.11 [-0.23, 0.02], 0.1047	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6767		0.9735		0.7728	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	6/28 (21.4)	6/40 (15.0)	4/26 (15.4)	11/91 (12.1)	10/54 (18.5)
RR [95%-CI]; p-value	0.46 [0.15, 1.37], 0.1611		0.98 [0.30, 3.13], 0.9660		0.65 [0.30, 1.43], 0.2883	
OR [95%-CI]; p-value	0.40 [0.11, 1.45], 0.1534		0.97 [0.25, 3.84], 0.9660		0.61 [0.24, 1.54], 0.2874	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1866		-0.00 [-0.18, 0.17], 0.9661		-0.06 [-0.19, 0.06], 0.3070	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	5/34 (14.7)	7/79 (8.9)	3/34 (8.8)	13/143 (9.1)	8/68 (11.8)
RR [95%-CI]; p-value	0.64 [0.21, 1.94], 0.4273		1.00 [0.28, 3.65], 0.9949		0.77 [0.34, 1.78], 0.5436	
OR [95%-CI]; p-value	0.60 [0.17, 2.13], 0.4262		1.00 [0.24, 4.14], 0.9949		0.75 [0.30, 1.91], 0.5443	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.09], 0.4517		0.00 [-0.11, 0.11], 0.9949		-0.03 [-0.12, 0.06], 0.5600	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.5637		0.7455		0.8072	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	3/28 (10.7)	3/40 (7.5)	2/26 (7.7)	4/91 (4.4)	5/54 (9.3)
RR [95%-CI]; p-value	0.18 [0.02, 1.68], 0.1330		0.98 [0.17, 5.44], 0.9770		0.47 [0.13, 1.69], 0.2506	
OR [95%-CI]; p-value	0.17 [0.02, 1.69], 0.0896		0.97 [0.15, 6.26], 0.9770		0.45 [0.12, 1.76], 0.2406	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1553		-0.00 [-0.13, 0.13], 0.9770		-0.05 [-0.14, 0.04], 0.2789	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	2/79 (2.5)	0/34 (0.0)	5/143 (3.5)	4/68 (5.9)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		1.75 [0.08, 37.75], 0.7220		0.59 [0.16, 2.14], 0.4267	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		1.77 [0.08, 40.21], 0.7178		0.58 [0.15, 2.23], 0.4228	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		0.01 [-0.04, 0.06], 0.6880		-0.02 [-0.09, 0.04], 0.4616	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5697		0.9948		0.7813	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	7/91 (7.7)	5/54 (9.3)
RR [95%-CI]; p-value	0.55 [0.12, 2.54], 0.4431		1.30 [0.26, 6.60], 0.7515		0.83 [0.28, 2.49], 0.7405	
OR [95%-CI]; p-value	0.52 [0.10, 2.77], 0.4381		1.33 [0.23, 7.86], 0.7500		0.82 [0.25, 2.71], 0.7406	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4714		0.02 [-0.12, 0.16], 0.7437		-0.02 [-0.11, 0.08], 0.7458	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	12/64 (18.8)	7/34 (20.6)	9/79 (11.4)	3/34 (8.8)	21/143 (14.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.91 [0.40, 2.10], 0.8261		1.29 [0.37, 4.48], 0.6871		1.00 [0.50, 2.00], 0.9969	
OR [95%-CI]; p-value	0.89 [0.31, 2.52], 0.8266		1.33 [0.34, 5.25], 0.6844		1.00 [0.44, 2.26], 0.9969	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.15], 0.8284		0.03 [-0.09, 0.14], 0.6704		-0.00 [-0.10, 0.10], 0.9969	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9746		0.9948		0.7928	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	4/28 (14.3)	3/40 (7.5)	2/26 (7.7)	6/91 (6.6)	6/54 (11.1)
RR [95%-CI]; p-value	0.41 [0.10, 1.71], 0.2220		0.98 [0.17, 5.44], 0.9770		0.59 [0.20, 1.75], 0.3437	
OR [95%-CI]; p-value	0.38 [0.08, 1.81], 0.2087		0.97 [0.15, 6.26], 0.9770		0.56 [0.17, 1.85], 0.3398	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2554		-0.00 [-0.13, 0.13], 0.9770		-0.05 [-0.14, 0.05], 0.3668	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	9/79 (11.4)	4/34 (11.8)	12/143 (8.4)	8/68 (11.8)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		0.97 [0.32, 2.93], 0.9546		0.71 [0.31, 1.66], 0.4342	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		0.96 [0.28, 3.38], 0.9546		0.69 [0.27, 1.77], 0.4344	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		-0.00 [-0.13, 0.13], 0.9549		-0.03 [-0.12, 0.06], 0.4578	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.1.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.3552		0.9073		0.5446	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	5/28 (17.9)	3/40 (7.5)	4/26 (15.4)	8/91 (8.8)	9/54 (16.7)
RR [95%-CI]; p-value	0.55 [0.17, 1.74], 0.3071		0.49 [0.12, 2.00], 0.3190		0.53 [0.22, 1.29], 0.1593	
OR [95%-CI]; p-value	0.50 [0.13, 1.90], 0.3031		0.45 [0.09, 2.18], 0.3094		0.48 [0.17, 1.34], 0.1541	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3348		-0.08 [-0.24, 0.08], 0.3369		-0.08 [-0.19, 0.04], 0.1802	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	3/34 (8.8)	3/79 (3.8)	3/34 (8.8)	10/143 (7.0)	6/68 (8.8)
RR [95%-CI]; p-value	1.24 [0.34, 4.49], 0.7436		0.43 [0.09, 2.03], 0.2861		0.79 [0.30, 2.09], 0.6385	
OR [95%-CI]; p-value	1.27 [0.31, 5.26], 0.7421		0.41 [0.08, 2.13], 0.2745		0.78 [0.27, 2.23], 0.6388	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7346		-0.05 [-0.15, 0.05], 0.3446		-0.02 [-0.10, 0.06], 0.6511	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_1_m_soc_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.3.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.2640		0.8453		0.5363	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	7/28 (25.0)	3/40 (7.5)	0/26 (0.0)	4/91 (4.4)	7/54 (13.0)
RR [95%-CI]; p-value	0.08 [0.01, 0.61], 0.0146		3.98 [0.21, 76.20], 0.3598		0.34 [0.10, 1.11], 0.0728	
OR [95%-CI]; p-value	0.06 [0.01, 0.52], 0.0012		4.22 [0.20, 87.76], 0.3156		0.31 [0.09, 1.11], 0.0596	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.07], 0.0062		0.06 [-0.04, 0.15], 0.2551		-0.09 [-0.18, 0.01], 0.0898	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	5/34 (14.7)	3/79 (3.8)	0/34 (0.0)	6/143 (4.2)	5/68 (7.4)
RR [95%-CI]; p-value	0.32 [0.08, 1.25], 0.1018		2.62 [0.13, 50.92], 0.5246		0.57 [0.18, 1.80], 0.3395	
OR [95%-CI]; p-value	0.29 [0.06, 1.28], 0.0847		2.68 [0.13, 55.06], 0.5057		0.55 [0.16, 1.88], 0.3350	
RD [95%-CI]; p-value	-0.10 [-0.23, 0.03], 0.1304		0.02 [-0.03, 0.08], 0.4277		-0.03 [-0.10, 0.04], 0.3781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_3_m_pt_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.3.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2065		0.7544		0.1905	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	4/28 (14.3)	2/40 (5.0)	1/26 (3.8)	2/91 (2.2)	5/54 (9.3)
RR [95%-CI]; p-value	0.07 [0.00, 1.24], 0.0695		1.30 [0.12, 13.62], 0.8267		0.24 [0.05, 1.18], 0.0790	
OR [95%-CI]; p-value	0.06 [0.00, 1.16], 0.0141		1.32 [0.11, 15.29], 0.8260		0.22 [0.04, 1.18], 0.0551	
RD [95%-CI]; p-value	-0.13 [-0.27, -0.00], 0.0486		0.01 [-0.09, 0.11], 0.8213		-0.07 [-0.15, 0.01], 0.0953	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	4/34 (11.8)	5/79 (6.3)	1/34 (2.9)	9/143 (6.3)	5/68 (7.4)
RR [95%-CI]; p-value	0.53 [0.14, 1.99], 0.3484		2.15 [0.26, 17.73], 0.4764		0.86 [0.30, 2.46], 0.7725	
OR [95%-CI]; p-value	0.50 [0.12, 2.14], 0.3426		2.23 [0.25, 19.84], 0.4613		0.85 [0.27, 2.63], 0.7727	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.07], 0.3814		0.03 [-0.04, 0.11], 0.3955		-0.01 [-0.08, 0.06], 0.7782	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_3_m_pt_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.3.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.4182		0.8266		0.4723	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	4/51 (7.8)	3/28 (10.7)	2/40 (5.0)	4/26 (15.4)	6/91 (6.6)	7/54 (13.0)
RR [95%-CI]; p-value	0.73 [0.18, 3.04], 0.6677		0.33 [0.06, 1.65], 0.1750		0.51 [0.18, 1.43], 0.2014	
OR [95%-CI]; p-value	0.71 [0.15, 3.42], 0.6675		0.29 [0.05, 1.71], 0.1516		0.47 [0.15, 1.49], 0.1943	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.11], 0.6796		-0.10 [-0.26, 0.05], 0.1870		-0.06 [-0.17, 0.04], 0.2259	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	1/34 (2.9)	2/79 (2.5)	2/34 (5.9)	6/143 (4.2)	3/68 (4.4)
RR [95%-CI]; p-value	2.13 [0.25, 18.27], 0.4923		0.43 [0.06, 2.93], 0.3890		0.95 [0.25, 3.69], 0.9421	
OR [95%-CI]; p-value	2.20 [0.24, 20.50], 0.4786		0.42 [0.06, 3.08], 0.3767		0.95 [0.23, 3.91], 0.9422	
RD [95%-CI]; p-value	0.03 [-0.05, 0.12], 0.4296		-0.03 [-0.12, 0.05], 0.4469		-0.00 [-0.06, 0.06], 0.9427	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_3_m_pt_ae10pct_age_pp.sas using SAS 9.4

Table 12.4.8.1.1.s1.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.7369		0.1990		0.2218	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	0/28 (0.0)	0/40 (0.0)	3/26 (11.5)	1/91 (1.1)	3/54 (5.6)
RR [95%-CI]; p-value	1.12 [0.04, 32.29], 0.9483		0.11 [0.01, 2.05], 0.1380		0.20 [0.02, 1.85], 0.1558	
OR [95%-CI]; p-value	1.12 [0.04, 34.45], 0.9483		0.10 [0.00, 2.00], 0.0663		0.19 [0.02, 1.86], 0.1132	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9475		-0.10 [-0.23, 0.02], 0.1130		-0.04 [-0.11, 0.02], 0.1773	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	1/34 (2.9)	2/79 (2.5)	0/34 (0.0)	3/143 (2.1)	1/68 (1.5)
RR [95%-CI]; p-value	0.53 [0.03, 8.23], 0.6510		1.75 [0.08, 37.75], 0.7220		1.43 [0.15, 13.46], 0.7564	
OR [95%-CI]; p-value	0.52 [0.03, 8.65], 0.6459		1.77 [0.08, 40.21], 0.7178		1.44 [0.15, 14.06], 0.7548	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.6748		0.01 [-0.04, 0.06], 0.6880		0.01 [-0.03, 0.04], 0.7398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_8_1_1_m_soc_sae5pct_age_pp.sas using SAS 9.4

Table 12.4.8.1.2.s1.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_8_1_2_m_pt_sae5pct_age_pp.sas using SAS 9.4

Table 12.4.5.1.1.s1.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_5_1_1_m_soc_aeg35pct_age_pp.sas using SAS 9.4

Table 12.4.5.1.2.s1.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_5_1_2_m_pt_aeg35pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.1383		0.1955		0.1489	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	9/28 (32.1)	10/40 (25.0)	5/26 (19.2)	16/91 (17.6)	14/54 (25.9)
RR [95%-CI]; p-value	0.37 [0.15, 0.92], 0.0331		1.30 [0.50, 3.37], 0.5896		0.68 [0.36, 1.28], 0.2295	
OR [95%-CI]; p-value	0.28 [0.09, 0.90], 0.0272		1.40 [0.42, 4.69], 0.5847		0.61 [0.27, 1.37], 0.2305	
RD [95%-CI]; p-value	-0.20 [-0.40, -0.01], 0.0398		0.06 [-0.14, 0.26], 0.5763		-0.08 [-0.22, 0.06], 0.2449	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	15/64 (23.4)	9/34 (26.5)	13/79 (16.5)	1/34 (2.9)	28/143 (19.6)	10/68 (14.7)
RR [95%-CI]; p-value	0.89 [0.43, 1.81], 0.7384		5.59 [0.76, 41.09], 0.0905		1.33 [0.69, 2.58], 0.3965	
OR [95%-CI]; p-value	0.85 [0.33, 2.21], 0.7396		6.50 [0.81, 51.84], 0.0455		1.41 [0.64, 3.11], 0.3892	
RD [95%-CI]; p-value	-0.03 [-0.21, 0.15], 0.7426		0.14 [0.04, 0.23], 0.0078		0.05 [-0.06, 0.16], 0.3691	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.6494		0.8121		0.9156	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	8/51 (15.7)	7/28 (25.0)	4/40 (10.0)	3/26 (11.5)	12/91 (13.2)	10/54 (18.5)
RR [95%-CI]; p-value	0.63 [0.25, 1.55], 0.3120		0.87 [0.21, 3.56], 0.8427		0.71 [0.33, 1.54], 0.3866	
OR [95%-CI]; p-value	0.56 [0.18, 1.75], 0.3127		0.85 [0.17, 4.16], 0.8428		0.67 [0.27, 1.67], 0.3869	
RD [95%-CI]; p-value	-0.09 [-0.28, 0.10], 0.3339		-0.02 [-0.17, 0.14], 0.8448		-0.05 [-0.18, 0.07], 0.4023	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	8/34 (23.5)	10/79 (12.7)	4/34 (11.8)	17/143 (11.9)	12/68 (17.6)
RR [95%-CI]; p-value	0.46 [0.18, 1.17], 0.1046		1.08 [0.36, 3.19], 0.8950		0.67 [0.34, 1.33], 0.2550	
OR [95%-CI]; p-value	0.40 [0.13, 1.22], 0.0994		1.09 [0.32, 3.74], 0.8948		0.63 [0.28, 1.41], 0.2562	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.04], 0.1272		0.01 [-0.12, 0.14], 0.8935		-0.06 [-0.16, 0.05], 0.2824	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1524		0.8272		0.3768	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	14/51 (27.5)	11/28 (39.3)	12/40 (30.0)	7/26 (26.9)	26/91 (28.6)	18/54 (33.3)
RR [95%-CI]; p-value	0.70 [0.37, 1.33], 0.2732		1.11 [0.51, 2.46], 0.7885		0.86 [0.52, 1.41], 0.5439	
OR [95%-CI]; p-value	0.58 [0.22, 1.55], 0.2793		1.16 [0.39, 3.49], 0.7873		0.80 [0.39, 1.65], 0.5465	
RD [95%-CI]; p-value	-0.12 [-0.34, 0.10], 0.2883		0.03 [-0.19, 0.25], 0.7858		-0.05 [-0.20, 0.11], 0.5504	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	17/64 (26.6)	6/34 (17.6)	16/79 (20.3)	7/34 (20.6)	33/143 (23.1)	13/68 (19.1)
RR [95%-CI]; p-value	1.51 [0.65, 3.46], 0.3357		0.98 [0.45, 2.17], 0.9676		1.21 [0.68, 2.14], 0.5198	
OR [95%-CI]; p-value	1.69 [0.60, 4.78], 0.3216		0.98 [0.36, 2.65], 0.9676		1.27 [0.62, 2.60], 0.5151	
RD [95%-CI]; p-value	0.09 [-0.08, 0.26], 0.2975		-0.00 [-0.17, 0.16], 0.9677		0.04 [-0.08, 0.16], 0.5043	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.8071		0.4451		0.3783	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	2/28 (7.1)	3/40 (7.5)	0/26 (0.0)	8/91 (8.8)	2/54 (3.7)
RR [95%-CI]; p-value	1.37 [0.28, 6.62], 0.6933		3.98 [0.21, 76.20], 0.3598		2.37 [0.52, 10.77], 0.2626	
OR [95%-CI]; p-value	1.41 [0.26, 7.80], 0.6905		4.22 [0.20, 87.76], 0.3156		2.51 [0.51, 12.26], 0.2425	
RD [95%-CI]; p-value	0.03 [-0.10, 0.15], 0.6778		0.06 [-0.04, 0.15], 0.2551		0.05 [-0.03, 0.13], 0.1951	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	3/34 (8.8)	5/79 (6.3)	2/34 (5.9)	11/143 (7.7)	5/68 (7.4)
RR [95%-CI]; p-value	1.06 [0.28, 3.99], 0.9284		1.08 [0.22, 5.28], 0.9281		1.05 [0.38, 2.89], 0.9307	
OR [95%-CI]; p-value	1.07 [0.25, 4.57], 0.9283		1.08 [0.20, 5.87], 0.9280		1.05 [0.35, 3.15], 0.9306	
RD [95%-CI]; p-value	0.01 [-0.11, 0.12], 0.9277		0.00 [-0.09, 0.10], 0.9270		0.00 [-0.07, 0.08], 0.9301	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0350		0.8073		0.0715	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	10/51 (19.6)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	14/91 (15.4)	5/54 (9.3)
RR [95%-CI]; p-value	1.83 [0.55, 6.11], 0.3256		1.30 [0.26, 6.60], 0.7515		1.66 [0.63, 4.36], 0.3019	
OR [95%-CI]; p-value	2.03 [0.51, 8.10], 0.3078		1.33 [0.23, 7.86], 0.7500		1.78 [0.60, 5.26], 0.2906	
RD [95%-CI]; p-value	0.09 [-0.07, 0.25], 0.2703		0.02 [-0.12, 0.16], 0.7437		0.06 [-0.05, 0.17], 0.2623	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	7/34 (20.6)	7/79 (8.9)	3/34 (8.8)	11/143 (7.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.30 [0.10, 0.96], 0.0432		1.00 [0.28, 3.65], 0.9949		0.52 [0.23, 1.17], 0.1152	
OR [95%-CI]; p-value	0.26 [0.07, 0.95], 0.0323		1.00 [0.24, 4.14], 0.9949		0.48 [0.19, 1.20], 0.1117	
RD [95%-CI]; p-value	-0.14 [-0.29, 0.00], 0.0581		0.00 [-0.11, 0.11], 0.9949		-0.07 [-0.16, 0.02], 0.1472	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8148		0.2299		0.2921	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	9/51 (17.6)	7/28 (25.0)	9/40 (22.5)	4/26 (15.4)	18/91 (19.8)	11/54 (20.4)
RR [95%-CI]; p-value	0.71 [0.29, 1.69], 0.4345		1.46 [0.50, 4.26], 0.4859		0.97 [0.50, 1.90], 0.9315	
OR [95%-CI]; p-value	0.64 [0.21, 1.97], 0.4366		1.60 [0.44, 5.85], 0.4776		0.96 [0.42, 2.23], 0.9316	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.12], 0.4517		0.07 [-0.12, 0.26], 0.4622		-0.01 [-0.14, 0.13], 0.9317	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	12/79 (15.2)	8/34 (23.5)	26/143 (18.2)	20/68 (29.4)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.65 [0.29, 1.44], 0.2832		0.62 [0.37, 1.03], 0.0627	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.58 [0.21, 1.59], 0.2867		0.53 [0.27, 1.05], 0.0648	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.08 [-0.25, 0.08], 0.3162		-0.11 [-0.24, 0.01], 0.0792	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.4870		0.8860		0.5472	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	8/28 (28.6)	5/40 (12.5)	5/26 (19.2)	11/91 (12.1)	13/54 (24.1)
RR [95%-CI]; p-value	0.41 [0.16, 1.07], 0.0680		0.65 [0.21, 2.03], 0.4577		0.50 [0.24, 1.04], 0.0640	
OR [95%-CI]; p-value	0.33 [0.10, 1.09], 0.0613		0.60 [0.16, 2.32], 0.4562		0.43 [0.18, 1.05], 0.0604	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0818		-0.07 [-0.25, 0.12], 0.4707		-0.12 [-0.25, 0.01], 0.0757	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	14/64 (21.9)	12/34 (35.3)	15/79 (19.0)	9/34 (26.5)	29/143 (20.3)	21/68 (30.9)
RR [95%-CI]; p-value	0.62 [0.32, 1.19], 0.1487		0.72 [0.35, 1.48], 0.3671		0.66 [0.41, 1.06], 0.0870	
OR [95%-CI]; p-value	0.51 [0.20, 1.29], 0.1521		0.65 [0.25, 1.68], 0.3724		0.57 [0.30, 1.10], 0.0905	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.06], 0.1660		-0.07 [-0.25, 0.10], 0.3929		-0.11 [-0.23, 0.02], 0.1047	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6767		0.9735		0.7728	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	6/28 (21.4)	6/40 (15.0)	4/26 (15.4)	11/91 (12.1)	10/54 (18.5)
RR [95%-CI]; p-value	0.46 [0.15, 1.37], 0.1611		0.98 [0.30, 3.13], 0.9660		0.65 [0.30, 1.43], 0.2883	
OR [95%-CI]; p-value	0.40 [0.11, 1.45], 0.1534		0.97 [0.25, 3.84], 0.9660		0.61 [0.24, 1.54], 0.2874	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1866		-0.00 [-0.18, 0.17], 0.9661		-0.06 [-0.19, 0.06], 0.3070	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	6/64 (9.4)	5/34 (14.7)	7/79 (8.9)	3/34 (8.8)	13/143 (9.1)	8/68 (11.8)
RR [95%-CI]; p-value	0.64 [0.21, 1.94], 0.4273		1.00 [0.28, 3.65], 0.9949		0.77 [0.34, 1.78], 0.5436	
OR [95%-CI]; p-value	0.60 [0.17, 2.13], 0.4262		1.00 [0.24, 4.14], 0.9949		0.75 [0.30, 1.91], 0.5443	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.09], 0.4517		0.00 [-0.11, 0.11], 0.9949		-0.03 [-0.12, 0.06], 0.5600	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5697		0.9948		0.7813	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	3/28 (10.7)	4/40 (10.0)	2/26 (7.7)	7/91 (7.7)	5/54 (9.3)
RR [95%-CI]; p-value	0.55 [0.12, 2.54], 0.4431		1.30 [0.26, 6.60], 0.7515		0.83 [0.28, 2.49], 0.7405	
OR [95%-CI]; p-value	0.52 [0.10, 2.77], 0.4381		1.33 [0.23, 7.86], 0.7500		0.82 [0.25, 2.71], 0.7406	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.08], 0.4714		0.02 [-0.12, 0.16], 0.7437		-0.02 [-0.11, 0.08], 0.7458	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	12/64 (18.8)	7/34 (20.6)	9/79 (11.4)	3/34 (8.8)	21/143 (14.7)	10/68 (14.7)
RR [95%-CI]; p-value	0.91 [0.40, 2.10], 0.8261		1.29 [0.37, 4.48], 0.6871		1.00 [0.50, 2.00], 0.9969	
OR [95%-CI]; p-value	0.89 [0.31, 2.52], 0.8266		1.33 [0.34, 5.25], 0.6844		1.00 [0.44, 2.26], 0.9969	
RD [95%-CI]; p-value	-0.02 [-0.18, 0.15], 0.8284		0.03 [-0.09, 0.14], 0.6704		-0.00 [-0.10, 0.10], 0.9969	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9746		0.9948		0.7928	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	3/51 (5.9)	4/28 (14.3)	3/40 (7.5)	2/26 (7.7)	6/91 (6.6)	6/54 (11.1)
RR [95%-CI]; p-value	0.41 [0.10, 1.71], 0.2220		0.98 [0.17, 5.44], 0.9770		0.59 [0.20, 1.75], 0.3437	
OR [95%-CI]; p-value	0.38 [0.08, 1.81], 0.2087		0.97 [0.15, 6.26], 0.9770		0.56 [0.17, 1.85], 0.3398	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.06], 0.2554		-0.00 [-0.13, 0.13], 0.9770		-0.05 [-0.14, 0.05], 0.3668	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	9/79 (11.4)	4/34 (11.8)	12/143 (8.4)	8/68 (11.8)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		0.97 [0.32, 2.93], 0.9546		0.71 [0.31, 1.66], 0.4342	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		0.96 [0.28, 3.38], 0.9546		0.69 [0.27, 1.77], 0.4344	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		-0.00 [-0.13, 0.13], 0.9549		-0.03 [-0.12, 0.06], 0.4578	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.2.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.3552		0.9073		0.5446	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	5/28 (17.9)	3/40 (7.5)	4/26 (15.4)	8/91 (8.8)	9/54 (16.7)
RR [95%-CI]; p-value	0.55 [0.17, 1.74], 0.3071		0.49 [0.12, 2.00], 0.3190		0.53 [0.22, 1.29], 0.1593	
OR [95%-CI]; p-value	0.50 [0.13, 1.90], 0.3031		0.45 [0.09, 2.18], 0.3094		0.48 [0.17, 1.34], 0.1541	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.08], 0.3348		-0.08 [-0.24, 0.08], 0.3369		-0.08 [-0.19, 0.04], 0.1802	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	7/64 (10.9)	3/34 (8.8)	3/79 (3.8)	3/34 (8.8)	10/143 (7.0)	6/68 (8.8)
RR [95%-CI]; p-value	1.24 [0.34, 4.49], 0.7436		0.43 [0.09, 2.03], 0.2861		0.79 [0.30, 2.09], 0.6385	
OR [95%-CI]; p-value	1.27 [0.31, 5.26], 0.7421		0.41 [0.08, 2.13], 0.2745		0.78 [0.27, 2.23], 0.6388	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7346		-0.05 [-0.15, 0.05], 0.3446		-0.02 [-0.10, 0.06], 0.6511	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_2_m_soc_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.4.s1.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.2640		0.8453		0.5363	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	1/51 (2.0)	7/28 (25.0)	3/40 (7.5)	0/26 (0.0)	4/91 (4.4)	7/54 (13.0)
RR [95%-CI]; p-value	0.08 [0.01, 0.61], 0.0146		3.98 [0.21, 76.20], 0.3598		0.34 [0.10, 1.11], 0.0728	
OR [95%-CI]; p-value	0.06 [0.01, 0.52], 0.0012		4.22 [0.20, 87.76], 0.3156		0.31 [0.09, 1.11], 0.0596	
RD [95%-CI]; p-value	-0.23 [-0.40, -0.07], 0.0062		0.06 [-0.04, 0.15], 0.2551		-0.09 [-0.18, 0.01], 0.0898	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	5/34 (14.7)	3/79 (3.8)	0/34 (0.0)	6/143 (4.2)	5/68 (7.4)
RR [95%-CI]; p-value	0.32 [0.08, 1.25], 0.1018		2.62 [0.13, 50.92], 0.5246		0.57 [0.18, 1.80], 0.3395	
OR [95%-CI]; p-value	0.29 [0.06, 1.28], 0.0847		2.68 [0.13, 55.06], 0.5057		0.55 [0.16, 1.88], 0.3350	
RD [95%-CI]; p-value	-0.10 [-0.23, 0.03], 0.1304		0.02 [-0.03, 0.08], 0.4277		-0.03 [-0.10, 0.04], 0.3781	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_4_m_pt_ae1pct_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.3303		0.9183		0.2782	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	8/91 (8.8)	2/54 (3.7)
RR [95%-CI]; p-value	6.71 [0.39, 115.74], 0.1904		0.65 [0.10, 4.33], 0.6562		2.37 [0.52, 10.77], 0.2626	
OR [95%-CI]; p-value	7.47 [0.40, 138.90], 0.1183		0.63 [0.08, 4.79], 0.6542		2.51 [0.51, 12.26], 0.2425	
RD [95%-CI]; p-value	0.10 [-0.00, 0.20], 0.0514		-0.03 [-0.15, 0.10], 0.6671		0.05 [-0.03, 0.13], 0.1951	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	5/64 (7.8)	2/34 (5.9)	4/79 (5.1)	3/34 (8.8)	9/143 (6.3)	5/68 (7.4)
RR [95%-CI]; p-value	1.33 [0.27, 6.49], 0.7259		0.57 [0.14, 2.43], 0.4503		0.86 [0.30, 2.46], 0.7725	
OR [95%-CI]; p-value	1.36 [0.25, 7.39], 0.7240		0.55 [0.12, 2.61], 0.4469		0.85 [0.27, 2.63], 0.7727	
RD [95%-CI]; p-value	0.02 [-0.08, 0.12], 0.7130		-0.04 [-0.14, 0.07], 0.4905		-0.01 [-0.08, 0.06], 0.7782	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7996		NA		0.8569	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	0/40 (0.0)	0/26 (0.0)	0/91 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	0/34 (0.0)	0/79 (0.0)	0/34 (0.0)	1/143 (0.7)	0/68 (0.0)
RR [95%-CI]; p-value	1.08 [0.04, 31.33], 0.9651		NA		0.96 [0.03, 28.21], 0.9802	
OR [95%-CI]; p-value	1.08 [0.04, 33.00], 0.9651		NA		0.96 [0.03, 28.90], 0.9802	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9647		NA		-0.00 [-0.02, 0.02], 0.9803	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2723		0.9183		0.2301	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	0/28 (0.0)	2/40 (5.0)	2/26 (7.7)	8/91 (8.8)	2/54 (3.7)
RR [95%-CI]; p-value	6.71 [0.39, 115.74], 0.1904		0.65 [0.10, 4.33], 0.6562		2.37 [0.52, 10.77], 0.2626	
OR [95%-CI]; p-value	7.47 [0.40, 138.90], 0.1183		0.63 [0.08, 4.79], 0.6542		2.51 [0.51, 12.26], 0.2425	
RD [95%-CI]; p-value	0.10 [-0.00, 0.20], 0.0514		-0.03 [-0.15, 0.10], 0.6671		0.05 [-0.03, 0.13], 0.1951	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	2/34 (5.9)	4/79 (5.1)	3/34 (8.8)	8/143 (5.6)	5/68 (7.4)
RR [95%-CI]; p-value	1.06 [0.20, 5.51], 0.9424		0.57 [0.14, 2.43], 0.4503		0.76 [0.26, 2.24], 0.6197	
OR [95%-CI]; p-value	1.07 [0.19, 6.14], 0.9424		0.55 [0.12, 2.61], 0.4469		0.75 [0.23, 2.37], 0.6195	
RD [95%-CI]; p-value	0.00 [-0.10, 0.10], 0.9419		-0.04 [-0.14, 0.07], 0.4905		-0.02 [-0.09, 0.05], 0.6349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8610		0.6708		0.6271	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	2/51 (3.9)	0/28 (0.0)	1/40 (2.5)	0/26 (0.0)	3/91 (3.3)	0/54 (0.0)
RR [95%-CI]; p-value	2.24 [0.10, 47.91], 0.6070		1.33 [0.05, 38.11], 0.8696		3.59 [0.18, 70.39], 0.3994	
OR [95%-CI]; p-value	2.29 [0.10, 52.47], 0.5954		1.33 [0.04, 41.20], 0.8690		3.68 [0.18, 74.92], 0.3646	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5544		0.01 [-0.06, 0.08], 0.8654		0.02 [-0.02, 0.07], 0.2954	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	1/34 (2.9)	0/79 (0.0)	0/34 (0.0)	3/143 (2.1)	1/68 (1.5)
RR [95%-CI]; p-value	1.59 [0.17, 14.74], 0.6813		NA		1.43 [0.15, 13.46], 0.7564	
OR [95%-CI]; p-value	1.62 [0.16, 16.23], 0.6775		NA		1.44 [0.15, 14.06], 0.7548	
RD [95%-CI]; p-value	0.02 [-0.06, 0.09], 0.6561		NA		0.01 [-0.03, 0.04], 0.7398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8058		0.3887		0.5479	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	5/28 (17.9)	3/40 (7.5)	1/26 (3.8)	9/91 (9.9)	6/54 (11.1)
RR [95%-CI]; p-value	0.66 [0.22, 1.97], 0.4545		1.95 [0.21, 17.75], 0.5534		0.89 [0.34, 2.36], 0.8153	
OR [95%-CI]; p-value	0.61 [0.17, 2.23], 0.4543		2.03 [0.20, 20.61], 0.5433		0.88 [0.29, 2.62], 0.8155	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4750		0.04 [-0.07, 0.15], 0.5155		-0.01 [-0.12, 0.09], 0.8178	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	4/64 (6.3)	4/34 (11.8)	6/79 (7.6)	4/34 (11.8)	10/143 (7.0)	8/68 (11.8)
RR [95%-CI]; p-value	0.53 [0.14, 1.99], 0.3484		0.65 [0.19, 2.14], 0.4746		0.59 [0.25, 1.44], 0.2486	
OR [95%-CI]; p-value	0.50 [0.12, 2.14], 0.3426		0.62 [0.16, 2.34], 0.4741		0.56 [0.21, 1.50], 0.2462	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.07], 0.3814		-0.04 [-0.16, 0.08], 0.5066		-0.05 [-0.13, 0.04], 0.2837	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.7996		0.6113		0.9129	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	0/51 (0.0)	0/28 (0.0)	1/40 (2.5)	0/26 (0.0)	1/91 (1.1)	0/54 (0.0)
RR [95%-CI]; p-value	NA		1.33 [0.05, 38.11], 0.8696		1.20 [0.04, 35.11], 0.9166	
OR [95%-CI]; p-value	NA		1.33 [0.04, 41.20], 0.8690		1.20 [0.04, 36.37], 0.9165	
RD [95%-CI]; p-value	NA		0.01 [-0.06, 0.08], 0.8654		0.00 [-0.03, 0.03], 0.9146	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	1/64 (1.6)	0/34 (0.0)	1/79 (1.3)	1/34 (2.9)	2/143 (1.4)	1/68 (1.5)
RR [95%-CI]; p-value	1.08 [0.04, 31.33], 0.9651		0.43 [0.03, 6.68], 0.5468		0.95 [0.09, 10.31], 0.9671	
OR [95%-CI]; p-value	1.08 [0.04, 33.00], 0.9651		0.42 [0.03, 6.97], 0.5356		0.95 [0.08, 10.67], 0.9671	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9647		-0.02 [-0.08, 0.05], 0.5959		-0.00 [-0.04, 0.03], 0.9674	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.5853		0.3201		0.3638	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	6/51 (11.8)	5/28 (17.9)	3/40 (7.5)	1/26 (3.8)	9/91 (9.9)	6/54 (11.1)
RR [95%-CI]; p-value	0.66 [0.22, 1.97], 0.4545		1.95 [0.21, 17.75], 0.5534		0.89 [0.34, 2.36], 0.8153	
OR [95%-CI]; p-value	0.61 [0.17, 2.23], 0.4543		2.03 [0.20, 20.61], 0.5433		0.88 [0.29, 2.62], 0.8155	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4750		0.04 [-0.07, 0.15], 0.5155		-0.01 [-0.12, 0.09], 0.8178	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	3/64 (4.7)	4/34 (11.8)	5/79 (6.3)	4/34 (11.8)	8/143 (5.6)	8/68 (11.8)
RR [95%-CI]; p-value	0.40 [0.09, 1.68], 0.2098		0.54 [0.15, 1.88], 0.3317		0.48 [0.19, 1.21], 0.1198	
OR [95%-CI]; p-value	0.37 [0.08, 1.75], 0.1954		0.51 [0.13, 2.02], 0.3277		0.44 [0.16, 1.24], 0.1136	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2479		-0.05 [-0.18, 0.07], 0.3781		-0.06 [-0.15, 0.02], 0.1565	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.7.s1.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9870		0.8370		0.7350	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	2/51 (3.9)	0/28 (0.0)	1/40 (2.5)	0/26 (0.0)	3/91 (3.3)	0/54 (0.0)
RR [95%-CI]; p-value	2.24 [0.10, 47.91], 0.6070		1.33 [0.05, 38.11], 0.8696		3.59 [0.18, 70.39], 0.3994	
OR [95%-CI]; p-value	2.29 [0.10, 52.47], 0.5954		1.33 [0.04, 41.20], 0.8690		3.68 [0.18, 74.92], 0.3646	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5544		0.01 [-0.06, 0.08], 0.8654		0.02 [-0.02, 0.07], 0.2954	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	2/64 (3.1)	0/34 (0.0)	2/79 (2.5)	1/34 (2.9)	4/143 (2.8)	1/68 (1.5)
RR [95%-CI]; p-value	2.16 [0.10, 46.51], 0.6239		0.86 [0.08, 9.18], 0.9012		1.90 [0.22, 16.70], 0.5618	
OR [95%-CI]; p-value	2.19 [0.10, 50.03], 0.6139		0.86 [0.08, 9.78], 0.9012		1.93 [0.21, 17.59], 0.5538	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5737		-0.00 [-0.07, 0.06], 0.9040		0.01 [-0.03, 0.05], 0.5088	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_7_m_pt_smq_age_pp.sas using SAS 9.4

Table 12.4.4.1.6.s1.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Age < 65 yrs vs 2.Age≥ 65 yrs

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.0911		0.5003		0.1762	
1.Age < 65 yrs	N1=51	N1=28	N1=40	N1=26	N1=91	N1=54
n/N1 (%)	5/51 (9.8)	10/28 (35.7)	11/40 (27.5)	5/26 (19.2)	16/91 (17.6)	15/54 (27.8)
RR [95%-CI]; p-value	0.27 [0.10, 0.72], 0.0090		1.43 [0.56, 3.64], 0.4533		0.63 [0.34, 1.18], 0.1474	
OR [95%-CI]; p-value	0.20 [0.06, 0.65], 0.0050		1.59 [0.48, 5.27], 0.4437		0.55 [0.25, 1.24], 0.1477	
RD [95%-CI]; p-value	-0.26 [-0.45, -0.06], 0.0093		0.08 [-0.12, 0.29], 0.4296		-0.10 [-0.24, 0.04], 0.1617	
2.Age ≥ 65 yrs	N2=64	N2=34	N2=79	N2=34	N2=143	N2=68
n/N2 (%)	11/64 (17.2)	7/34 (20.6)	12/79 (15.2)	2/34 (5.9)	23/143 (16.1)	9/68 (13.2)
RR [95%-CI]; p-value	0.83 [0.36, 1.96], 0.6777		2.58 [0.61, 10.92], 0.1972		1.22 [0.59, 2.48], 0.5928	
OR [95%-CI]; p-value	0.80 [0.28, 2.30], 0.6790		2.87 [0.61, 13.57], 0.1684		1.26 [0.55, 2.89], 0.5898	
RD [95%-CI]; p-value	-0.03 [-0.20, 0.13], 0.6851		0.09 [-0.02, 0.20], 0.1030		0.03 [-0.07, 0.13], 0.5788	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s1_age_pp/T12_4_4_1_6_m_pt_adr_age_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.2897		0.1542		0.0696	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	49/59 (83.1)	25/29 (86.2)	40/59 (67.8)	18/31 (58.1)	89/118 (75.4)	43/60 (71.7)
RR [95%-CI]; p-value	0.96 [0.80, 1.16], 0.6938		1.17 [0.83, 1.65], 0.3815		1.05 [0.87, 1.27], 0.5972	
OR [95%-CI]; p-value	0.78 [0.22, 2.75], 0.7036		1.52 [0.62, 3.73], 0.3594		1.21 [0.60, 2.44], 0.5883	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.13], 0.6951		0.10 [-0.11, 0.31], 0.3653		0.04 [-0.10, 0.18], 0.5935	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	34/56 (60.7)	25/33 (75.8)	32/60 (53.3)	19/29 (65.5)	66/116 (56.9)	44/62 (71.0)
RR [95%-CI]; p-value	0.80 [0.60, 1.07], 0.1289		0.81 [0.57, 1.16], 0.2554		0.80 [0.64, 1.00], 0.0538	
OR [95%-CI]; p-value	0.49 [0.19, 1.29], 0.1470		0.60 [0.24, 1.51], 0.2761		0.54 [0.28, 1.04], 0.0656	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.04], 0.1291		-0.12 [-0.34, 0.09], 0.2648		-0.14 [-0.29, 0.00], 0.0564	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.5846		0.5383		0.7579	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	7/59 (11.9)	6/29 (20.7)	5/59 (8.5)	0/31 (0.0)	12/118 (10.2)	6/60 (10.0)
RR [95%-CI]; p-value	0.57 [0.21, 1.55], 0.2737		5.34 [0.30, 94.61], 0.2534		1.02 [0.40, 2.58], 0.9717	
OR [95%-CI]; p-value	0.52 [0.16, 1.71], 0.2728		5.74 [0.30, 108.64], 0.1914		1.02 [0.36, 2.86], 0.9717	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.08], 0.3059		0.07 [-0.01, 0.15], 0.1055		0.00 [-0.09, 0.10], 0.9716	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	4/33 (12.1)	8/60 (13.3)	2/29 (6.9)	14/116 (12.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.88 [0.27, 2.90], 0.8389		1.93 [0.44, 8.53], 0.3842		1.25 [0.50, 3.08], 0.6326	
OR [95%-CI]; p-value	0.87 [0.23, 3.34], 0.8391		2.08 [0.41, 10.47], 0.3675		1.28 [0.47, 3.52], 0.6303	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.12], 0.8413		0.06 [-0.06, 0.19], 0.3171		0.02 [-0.07, 0.12], 0.6199	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.4637		0.8913		0.5475	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	1/29 (3.4)	1/59 (1.7)	2/31 (6.5)	7/118 (5.9)	3/60 (5.0)
RR [95%-CI]; p-value	2.95 [0.37, 23.37], 0.3058		0.26 [0.02, 2.78], 0.2671		1.19 [0.32, 4.43], 0.7991	
OR [95%-CI]; p-value	3.17 [0.36, 27.65], 0.2734		0.25 [0.02, 2.87], 0.2323		1.20 [0.30, 4.81], 0.7985	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1955		-0.05 [-0.14, 0.04], 0.3137		0.01 [-0.06, 0.08], 0.7932	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	3/33 (9.1)	2/60 (3.3)	3/29 (10.3)	8/116 (6.9)	6/62 (9.7)
RR [95%-CI]; p-value	1.18 [0.32, 4.40], 0.8069		0.32 [0.06, 1.82], 0.2004		0.71 [0.26, 1.96], 0.5120	
OR [95%-CI]; p-value	1.20 [0.28, 5.16], 0.8062		0.30 [0.05, 1.90], 0.1782		0.69 [0.23, 2.09], 0.5114	
RD [95%-CI]; p-value	0.02 [-0.11, 0.14], 0.8025		-0.07 [-0.19, 0.05], 0.2513		-0.03 [-0.11, 0.06], 0.5303	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.0994		0.7281		0.2424	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	11/59 (18.6)	2/29 (6.9)	4/59 (6.8)	3/31 (9.7)	15/118 (12.7)	5/60 (8.3)
RR [95%-CI]; p-value	2.70 [0.64, 11.41], 0.1757		0.70 [0.17, 2.93], 0.6263		1.53 [0.58, 4.00], 0.3902	
OR [95%-CI]; p-value	3.09 [0.64, 15.00], 0.1443		0.68 [0.14, 3.25], 0.6257		1.60 [0.55, 4.64], 0.3819	
RD [95%-CI]; p-value	0.12 [-0.02, 0.25], 0.0895		-0.03 [-0.15, 0.09], 0.6422		0.04 [-0.05, 0.14], 0.3520	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	8/33 (24.2)	8/60 (13.3)	4/29 (13.8)	17/116 (14.7)	12/62 (19.4)
RR [95%-CI]; p-value	0.66 [0.28, 1.55], 0.3430		0.97 [0.32, 2.95], 0.9525		0.76 [0.39, 1.48], 0.4169	
OR [95%-CI]; p-value	0.60 [0.21, 1.74], 0.3435		0.96 [0.26, 3.50], 0.9525		0.72 [0.32, 1.61], 0.4186	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.09], 0.3602		-0.00 [-0.16, 0.15], 0.9528		-0.05 [-0.16, 0.07], 0.4332	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.0699		0.8820		0.1018	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	3/29 (10.3)	2/59 (3.4)	0/31 (0.0)	4/118 (3.4)	3/60 (5.0)
RR [95%-CI]; p-value	0.33 [0.06, 1.85], 0.2070		2.14 [0.10, 45.94], 0.6279		0.68 [0.16, 2.93], 0.6029	
OR [95%-CI]; p-value	0.30 [0.05, 1.93], 0.1852		2.18 [0.10, 49.75], 0.6182		0.67 [0.14, 3.08], 0.6014	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2563		0.02 [-0.05, 0.08], 0.5782		-0.02 [-0.08, 0.05], 0.6224	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	0/33 (0.0)	3/60 (5.0)	0/29 (0.0)	9/116 (7.8)	0/62 (0.0)
RR [95%-CI]; p-value	7.18 [0.41, 124.48], 0.1757		2.95 [0.15, 57.00], 0.4740		9.70 [0.57, 164.52], 0.1158	
OR [95%-CI]; p-value	7.92 [0.43, 146.60], 0.1038		3.05 [0.15, 63.00], 0.4483		10.43 [0.59, 183.02], 0.0482	
RD [95%-CI]; p-value	0.09 [0.00, 0.18], 0.0466		0.03 [-0.04, 0.11], 0.3695		0.07 [0.02, 0.12], 0.0107	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.5125		NA		0.5527	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	1/29 (3.4)	0/59 (0.0)	0/31 (0.0)	0/118 (0.0)	1/60 (1.7)
RR [95%-CI]; p-value	0.24 [0.01, 7.06], 0.4110		NA		0.25 [0.01, 7.44], 0.4258	
OR [95%-CI]; p-value	0.24 [0.01, 7.29], 0.3723		NA		0.25 [0.01, 7.56], 0.3895	
RD [95%-CI]; p-value	-0.03 [-0.10, 0.04], 0.4674		NA		-0.01 [-0.05, 0.02], 0.4786	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	0/60 (0.0)	0/29 (0.0)	1/116 (0.9)	0/62 (0.0)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		NA		1.08 [0.04, 31.67], 0.9654	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		NA		1.08 [0.04, 32.59], 0.9654	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		NA		0.00 [-0.03, 0.03], 0.9650	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7350		NA		0.7758	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	1/29 (3.4)	0/59 (0.0)	0/31 (0.0)	0/118 (0.0)	1/60 (1.7)
RR [95%-CI]; p-value	0.24 [0.01, 7.06], 0.4110		NA		0.25 [0.01, 7.44], 0.4258	
OR [95%-CI]; p-value	0.24 [0.01, 7.29], 0.3723		NA		0.25 [0.01, 7.56], 0.3895	
RD [95%-CI]; p-value	-0.03 [-0.10, 0.04], 0.4674		NA		-0.01 [-0.05, 0.02], 0.4786	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	0/56 (0.0)	0/33 (0.0)	0/60 (0.0)	0/29 (0.0)	0/116 (0.0)	0/62 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.1009		0.3767		0.0847	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	44/59 (74.6)	23/29 (79.3)	32/59 (54.2)	14/31 (45.2)	76/118 (64.4)	37/60 (61.7)
RR [95%-CI]; p-value	0.94 [0.74, 1.19], 0.6126		1.20 [0.76, 1.89], 0.4284		1.04 [0.82, 1.33], 0.7230	
OR [95%-CI]; p-value	0.77 [0.26, 2.24], 0.6243		1.44 [0.60, 3.45], 0.4131		1.12 [0.59, 2.14], 0.7197	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.14], 0.6152		0.09 [-0.13, 0.31], 0.4112		0.03 [-0.12, 0.18], 0.7209	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	24/56 (42.9)	22/33 (66.7)	28/60 (46.7)	15/29 (51.7)	52/116 (44.8)	37/62 (59.7)
RR [95%-CI]; p-value	0.64 [0.44, 0.95], 0.0252		0.90 [0.58, 1.41], 0.6494		0.75 [0.56, 1.00], 0.0511	
OR [95%-CI]; p-value	0.38 [0.15, 0.92], 0.0299		0.82 [0.34, 1.98], 0.6545		0.55 [0.29, 1.03], 0.0590	
RD [95%-CI]; p-value	-0.24 [-0.44, -0.03], 0.0239		-0.05 [-0.27, 0.17], 0.6543		-0.15 [-0.30, 0.00], 0.0555	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.1886		0.0296		0.0091	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	19/59 (32.2)	8/29 (27.6)	23/59 (39.0)	6/31 (19.4)	42/118 (35.6)	14/60 (23.3)
RR [95%-CI]; p-value	1.17 [0.58, 2.34], 0.6631		2.01 [0.92, 4.42], 0.0809		1.53 [0.91, 2.56], 0.1107	
OR [95%-CI]; p-value	1.25 [0.47, 3.32], 0.6589		2.66 [0.95, 7.48], 0.0583		1.82 [0.90, 3.68], 0.0959	
RD [95%-CI]; p-value	0.05 [-0.16, 0.25], 0.6537		0.20 [0.01, 0.38], 0.0393		0.12 [-0.01, 0.26], 0.0806	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	19/56 (33.9)	17/33 (51.5)	13/60 (21.7)	10/29 (34.5)	32/116 (27.6)	27/62 (43.5)
RR [95%-CI]; p-value	0.66 [0.40, 1.08], 0.0969		0.63 [0.31, 1.26], 0.1901		0.63 [0.42, 0.95], 0.0287	
OR [95%-CI]; p-value	0.48 [0.20, 1.16], 0.1025		0.53 [0.20, 1.40], 0.1955		0.49 [0.26, 0.94], 0.0311	
RD [95%-CI]; p-value	-0.18 [-0.39, 0.03], 0.1021		-0.13 [-0.33, 0.07], 0.2136		-0.16 [-0.31, -0.01], 0.0343	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s2.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.4637		0.8913		0.5475	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	1/29 (3.4)	1/59 (1.7)	2/31 (6.5)	7/118 (5.9)	3/60 (5.0)
RR [95%-CI]; p-value	2.95 [0.37, 23.37], 0.3058		0.26 [0.02, 2.78], 0.2671		1.19 [0.32, 4.43], 0.7991	
OR [95%-CI]; p-value	3.17 [0.36, 27.65], 0.2734		0.25 [0.02, 2.87], 0.2323		1.20 [0.30, 4.81], 0.7985	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1955		-0.05 [-0.14, 0.04], 0.3137		0.01 [-0.06, 0.08], 0.7932	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	3/33 (9.1)	2/60 (3.3)	3/29 (10.3)	8/116 (6.9)	6/62 (9.7)
RR [95%-CI]; p-value	1.18 [0.32, 4.40], 0.8069		0.32 [0.06, 1.82], 0.2004		0.71 [0.26, 1.96], 0.5120	
OR [95%-CI]; p-value	1.20 [0.28, 5.16], 0.8062		0.30 [0.05, 1.90], 0.1782		0.69 [0.23, 2.09], 0.5114	
RD [95%-CI]; p-value	0.02 [-0.11, 0.14], 0.8025		-0.07 [-0.19, 0.05], 0.2513		-0.03 [-0.11, 0.06], 0.5303	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_3_1_m_sf_ttl_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.5890		0.8138		0.3322	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	2/29 (6.9)	4/59 (6.8)	1/31 (3.2)	7/118 (5.9)	3/60 (5.0)
RR [95%-CI]; p-value	0.74 [0.13, 4.17], 0.7303		2.10 [0.25, 18.00], 0.4979		1.19 [0.32, 4.43], 0.7991	
OR [95%-CI]; p-value	0.72 [0.11, 4.59], 0.7300		2.18 [0.23, 20.41], 0.4843		1.20 [0.30, 4.81], 0.7985	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7421		0.04 [-0.05, 0.12], 0.4356		0.01 [-0.06, 0.08], 0.7932	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	7/33 (21.2)	3/60 (5.0)	1/29 (3.4)	8/116 (6.9)	8/62 (12.9)
RR [95%-CI]; p-value	0.42 [0.15, 1.22], 0.1109		1.45 [0.16, 13.34], 0.7428		0.53 [0.21, 1.35], 0.1869	
OR [95%-CI]; p-value	0.36 [0.11, 1.26], 0.1012		1.47 [0.15, 14.82], 0.7405		0.50 [0.18, 1.40], 0.1819	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1281		0.02 [-0.07, 0.10], 0.7246		-0.06 [-0.16, 0.04], 0.2169	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.8363		0.6883		0.9003	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	10/29 (34.5)	13/59 (22.0)	3/31 (9.7)	25/118 (21.2)	13/60 (21.7)
RR [95%-CI]; p-value	0.59 [0.29, 1.20], 0.1461		2.28 [0.70, 7.39], 0.1709		0.98 [0.54, 1.77], 0.9410	
OR [95%-CI]; p-value	0.49 [0.18, 1.31], 0.1498		2.64 [0.69, 10.08], 0.1451		0.97 [0.46, 2.07], 0.9411	
RD [95%-CI]; p-value	-0.14 [-0.34, 0.06], 0.1682		0.12 [-0.02, 0.27], 0.1026		-0.00 [-0.13, 0.12], 0.9412	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	8/33 (24.2)	10/60 (16.7)	3/29 (10.3)	19/116 (16.4)	11/62 (17.7)
RR [95%-CI]; p-value	0.66 [0.28, 1.55], 0.3430		1.61 [0.48, 5.41], 0.4404		0.92 [0.47, 1.81], 0.8166	
OR [95%-CI]; p-value	0.60 [0.21, 1.74], 0.3435		1.73 [0.44, 6.85], 0.4287		0.91 [0.40, 2.05], 0.8170	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.09], 0.3602		0.06 [-0.08, 0.21], 0.3945		-0.01 [-0.13, 0.10], 0.8187	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8968		0.2880		0.4617	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	8/59 (13.6)	7/29 (24.1)	7/59 (11.9)	2/31 (6.5)	15/118 (12.7)	9/60 (15.0)
RR [95%-CI]; p-value	0.56 [0.23, 1.40], 0.2151		1.84 [0.41, 8.33], 0.4291		0.85 [0.39, 1.82], 0.6718	
OR [95%-CI]; p-value	0.49 [0.16, 1.53], 0.2148		1.95 [0.38, 10.02], 0.4160		0.83 [0.34, 2.01], 0.6726	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2456		0.05 [-0.07, 0.17], 0.3748		-0.02 [-0.13, 0.09], 0.6794	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	7/56 (12.5)	8/33 (24.2)	7/60 (11.7)	5/29 (17.2)	14/116 (12.1)	13/62 (21.0)
RR [95%-CI]; p-value	0.52 [0.21, 1.29], 0.1576		0.68 [0.23, 1.95], 0.4696		0.58 [0.29, 1.15], 0.1162	
OR [95%-CI]; p-value	0.45 [0.15, 1.37], 0.1529		0.63 [0.18, 2.20], 0.4705		0.52 [0.23, 1.18], 0.1148	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1757		-0.06 [-0.22, 0.10], 0.4938		-0.09 [-0.21, 0.03], 0.1374	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1251		0.8903		0.2081	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	22/59 (37.3)	8/29 (27.6)	18/59 (30.5)	9/31 (29.0)	40/118 (33.9)	17/60 (28.3)
RR [95%-CI]; p-value	1.35 [0.69, 2.66], 0.3824		1.05 [0.54, 2.06], 0.8849		1.20 [0.74, 1.92], 0.4591	
OR [95%-CI]; p-value	1.56 [0.59, 4.12], 0.3668		1.07 [0.41, 2.78], 0.8845		1.30 [0.66, 2.56], 0.4519	
RD [95%-CI]; p-value	0.10 [-0.11, 0.30], 0.3517		0.01 [-0.18, 0.21], 0.8840		0.06 [-0.09, 0.20], 0.4439	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	9/33 (27.3)	10/60 (16.7)	5/29 (17.2)	19/116 (16.4)	14/62 (22.6)
RR [95%-CI]; p-value	0.59 [0.26, 1.33], 0.2049		0.97 [0.36, 2.57], 0.9458		0.73 [0.39, 1.35], 0.3083	
OR [95%-CI]; p-value	0.51 [0.18, 1.45], 0.2038		0.96 [0.30, 3.12], 0.9459		0.67 [0.31, 1.45], 0.3104	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2222		-0.01 [-0.17, 0.16], 0.9461		-0.06 [-0.19, 0.06], 0.3269	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0634		0.7700		0.1043	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	10/59 (16.9)	3/29 (10.3)	5/59 (8.5)	2/31 (6.5)	15/118 (12.7)	5/60 (8.3)
RR [95%-CI]; p-value	1.64 [0.49, 5.50], 0.4243		1.31 [0.27, 6.38], 0.7353		1.53 [0.58, 4.00], 0.3902	
OR [95%-CI]; p-value	1.77 [0.45, 7.00], 0.4118		1.34 [0.25, 7.35], 0.7335		1.60 [0.55, 4.64], 0.3819	
RD [95%-CI]; p-value	0.07 [-0.08, 0.21], 0.3768		0.02 [-0.09, 0.13], 0.7232		0.04 [-0.05, 0.14], 0.3520	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	4/56 (7.1)	7/33 (21.2)	6/60 (10.0)	3/29 (10.3)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.34 [0.11, 1.06], 0.0637		0.97 [0.26, 3.59], 0.9596		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.29 [0.08, 1.06], 0.0514		0.96 [0.22, 4.16], 0.9597		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.14 [-0.30, 0.01], 0.0751		-0.00 [-0.14, 0.13], 0.9599		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0352		0.2680		0.3792	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	15/59 (25.4)	6/29 (20.7)	8/59 (13.6)	7/31 (22.6)	23/118 (19.5)	13/60 (21.7)
RR [95%-CI]; p-value	1.23 [0.53, 2.83], 0.6290		0.60 [0.24, 1.50], 0.2754		0.90 [0.49, 1.65], 0.7318	
OR [95%-CI]; p-value	1.31 [0.45, 3.82], 0.6243		0.54 [0.17, 1.66], 0.2752		0.88 [0.41, 1.88], 0.7327	
RD [95%-CI]; p-value	0.05 [-0.14, 0.23], 0.6152		-0.09 [-0.26, 0.08], 0.3016		-0.02 [-0.15, 0.10], 0.7359	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	13/33 (39.4)	13/60 (21.7)	5/29 (17.2)	21/116 (18.1)	18/62 (29.0)
RR [95%-CI]; p-value	0.36 [0.17, 0.78], 0.0097		1.26 [0.50, 3.19], 0.6306		0.62 [0.36, 1.08], 0.0917	
OR [95%-CI]; p-value	0.26 [0.09, 0.71], 0.0070		1.33 [0.42, 4.16], 0.6262		0.54 [0.26, 1.11], 0.0931	
RD [95%-CI]; p-value	-0.25 [-0.44, -0.06], 0.0097		0.04 [-0.13, 0.22], 0.6152		-0.11 [-0.24, 0.02], 0.1071	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.9665		0.0630		0.1769	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	11/29 (37.9)	14/59 (23.7)	6/31 (19.4)	26/118 (22.0)	17/60 (28.3)
RR [95%-CI]; p-value	0.54 [0.27, 1.07], 0.0753		1.23 [0.52, 2.87], 0.6392		0.78 [0.46, 1.32], 0.3492	
OR [95%-CI]; p-value	0.42 [0.16, 1.12], 0.0775		1.30 [0.44, 3.79], 0.6353		0.71 [0.35, 1.45], 0.3533	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.03], 0.0915		0.04 [-0.13, 0.22], 0.6270		-0.06 [-0.20, 0.07], 0.3652	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	9/33 (27.3)	6/60 (10.0)	8/29 (27.6)	14/116 (12.1)	17/62 (27.4)
RR [95%-CI]; p-value	0.52 [0.22, 1.23], 0.1358		0.36 [0.14, 0.95], 0.0385		0.44 [0.23, 0.83], 0.0115	
OR [95%-CI]; p-value	0.44 [0.15, 1.30], 0.1322		0.29 [0.09, 0.94], 0.0327		0.36 [0.16, 0.80], 0.0101	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1514		-0.18 [-0.36, 0.00], 0.0548		-0.15 [-0.28, -0.03], 0.0168	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8198		0.3494		0.6250	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	6/29 (20.7)	8/59 (13.6)	3/31 (9.7)	14/118 (11.9)	9/60 (15.0)
RR [95%-CI]; p-value	0.49 [0.17, 1.39], 0.1810		1.40 [0.40, 4.91], 0.5980		0.79 [0.36, 1.72], 0.5545	
OR [95%-CI]; p-value	0.43 [0.13, 1.49], 0.1765		1.46 [0.36, 5.97], 0.5932		0.76 [0.31, 1.88], 0.5555	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.06], 0.2153		0.04 [-0.10, 0.17], 0.5755		-0.03 [-0.14, 0.08], 0.5677	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	5/33 (15.2)	5/60 (8.3)	4/29 (13.8)	10/116 (8.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.59 [0.18, 1.88], 0.3726		0.60 [0.18, 2.08], 0.4249		0.59 [0.25, 1.38], 0.2274	
OR [95%-CI]; p-value	0.55 [0.15, 2.06], 0.3692		0.57 [0.14, 2.30], 0.4233		0.56 [0.21, 1.45], 0.2249	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.08], 0.3948		-0.05 [-0.20, 0.09], 0.4564		-0.06 [-0.16, 0.04], 0.2548	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3714		0.8456		0.6672	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	3/29 (10.3)	2/59 (3.4)	1/31 (3.2)	5/118 (4.2)	4/60 (6.7)
RR [95%-CI]; p-value	0.49 [0.11, 2.29], 0.3652		1.05 [0.10, 11.14], 0.9672		0.64 [0.18, 2.28], 0.4869	
OR [95%-CI]; p-value	0.46 [0.09, 2.46], 0.3575		1.05 [0.09, 12.09], 0.9671		0.62 [0.16, 2.40], 0.4844	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4065		0.00 [-0.08, 0.08], 0.9669		-0.02 [-0.10, 0.05], 0.5133	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	4/33 (12.1)	3/60 (5.0)	1/29 (3.4)	4/116 (3.4)	5/62 (8.1)
RR [95%-CI]; p-value	0.15 [0.02, 1.26], 0.0806		1.45 [0.16, 13.34], 0.7428		0.43 [0.12, 1.53], 0.1926	
OR [95%-CI]; p-value	0.13 [0.01, 1.23], 0.0408		1.47 [0.15, 14.82], 0.7405		0.41 [0.11, 1.58], 0.1805	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0824		0.02 [-0.07, 0.10], 0.7246		-0.05 [-0.12, 0.03], 0.2306	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.6761		0.2140		0.5381	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	7/59 (11.9)	5/29 (17.2)	9/59 (15.3)	2/31 (6.5)	16/118 (13.6)	7/60 (11.7)
RR [95%-CI]; p-value	0.69 [0.24, 1.98], 0.4887		2.36 [0.54, 10.28], 0.2510		1.16 [0.51, 2.67], 0.7232	
OR [95%-CI]; p-value	0.65 [0.19, 2.24], 0.4896		2.61 [0.53, 12.91], 0.2257		1.19 [0.46, 3.07], 0.7220	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5110		0.09 [-0.04, 0.21], 0.1712		0.02 [-0.08, 0.12], 0.7162	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	5/33 (15.2)	4/60 (6.7)	3/29 (10.3)	12/116 (10.3)	8/62 (12.9)
RR [95%-CI]; p-value	0.94 [0.34, 2.64], 0.9110		0.64 [0.15, 2.69], 0.5470		0.80 [0.35, 1.86], 0.6060	
OR [95%-CI]; p-value	0.93 [0.28, 3.13], 0.9111		0.62 [0.13, 2.97], 0.5457		0.78 [0.30, 2.02], 0.6066	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9116		-0.04 [-0.16, 0.09], 0.5719		-0.03 [-0.13, 0.07], 0.6167	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3473		0.0953		0.0572	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	4/59 (6.8)	3/29 (10.3)	6/59 (10.2)	0/31 (0.0)	10/118 (8.5)	3/60 (5.0)
RR [95%-CI]; p-value	0.66 [0.16, 2.74], 0.5623		6.41 [0.37, 111.02], 0.2019		1.69 [0.48, 5.93], 0.4089	
OR [95%-CI]; p-value	0.63 [0.13, 3.02], 0.5613		7.02 [0.38, 129.99], 0.1320		1.76 [0.47, 6.65], 0.3997	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.09], 0.5853		0.09 [-0.00, 0.17], 0.0577		0.03 [-0.04, 0.11], 0.3614	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	5/33 (15.2)	6/60 (10.0)	6/29 (20.7)	8/116 (6.9)	11/62 (17.7)
RR [95%-CI]; p-value	0.24 [0.05, 1.15], 0.0735		0.48 [0.17, 1.37], 0.1711		0.39 [0.16, 0.92], 0.0307	
OR [95%-CI]; p-value	0.21 [0.04, 1.14], 0.0500		0.43 [0.12, 1.46], 0.1664		0.34 [0.13, 0.91], 0.0256	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0847		-0.11 [-0.27, 0.06], 0.2064		-0.11 [-0.21, -0.00], 0.0443	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.1.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8323		0.3804		0.5422	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	4/29 (13.8)	2/59 (3.4)	1/31 (3.2)	8/118 (6.8)	5/60 (8.3)
RR [95%-CI]; p-value	0.74 [0.23, 2.41], 0.6140		1.05 [0.10, 11.14], 0.9672		0.81 [0.28, 2.38], 0.7063	
OR [95%-CI]; p-value	0.71 [0.18, 2.73], 0.6146		1.05 [0.09, 12.09], 0.9671		0.80 [0.25, 2.56], 0.7065	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6297		0.00 [-0.08, 0.08], 0.9669		-0.02 [-0.10, 0.07], 0.7149	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	4/33 (12.1)	4/60 (6.7)	6/29 (20.7)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.88 [0.27, 2.90], 0.8389		0.32 [0.10, 1.05], 0.0610		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.87 [0.23, 3.34], 0.8391		0.27 [0.07, 1.06], 0.0496		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.12], 0.8413		-0.14 [-0.30, 0.02], 0.0866		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_1_m_soc_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.3.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4387		0.9692		0.3829	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	8/29 (27.6)	3/59 (5.1)	0/31 (0.0)	5/118 (4.2)	8/60 (13.3)
RR [95%-CI]; p-value	0.12 [0.03, 0.54], 0.0056		3.20 [0.17, 61.97], 0.4412		0.32 [0.11, 0.93], 0.0363	
OR [95%-CI]; p-value	0.09 [0.02, 0.47], 0.0008		3.32 [0.16, 68.46], 0.4111		0.29 [0.09, 0.92], 0.0275	
RD [95%-CI]; p-value	-0.24 [-0.41, -0.07], 0.0050		0.03 [-0.04, 0.11], 0.3346		-0.09 [-0.18, 0.00], 0.0562	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	4/33 (12.1)	3/60 (5.0)	0/29 (0.0)	5/116 (4.3)	4/62 (6.5)
RR [95%-CI]; p-value	0.29 [0.06, 1.52], 0.1447		2.95 [0.15, 57.00], 0.4740		0.67 [0.19, 2.40], 0.5363	
OR [95%-CI]; p-value	0.27 [0.05, 1.56], 0.1202		3.05 [0.15, 63.00], 0.4483		0.65 [0.17, 2.53], 0.5345	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1678		0.03 [-0.04, 0.11], 0.3695		-0.02 [-0.09, 0.05], 0.5570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_3_m_pt_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.3.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2827		0.5501		0.5543	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	3/29 (10.3)	4/59 (6.8)	2/31 (6.5)	7/118 (5.9)	5/60 (8.3)
RR [95%-CI]; p-value	0.49 [0.11, 2.29], 0.3652		1.05 [0.20, 5.42], 0.9528		0.71 [0.24, 2.15], 0.5465	
OR [95%-CI]; p-value	0.46 [0.09, 2.46], 0.3575		1.05 [0.18, 6.10], 0.9527		0.69 [0.21, 2.29], 0.5459	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4065		0.00 [-0.10, 0.11], 0.9524		-0.02 [-0.11, 0.06], 0.5655	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	5/33 (15.2)	3/60 (5.0)	0/29 (0.0)	4/116 (3.4)	5/62 (8.1)
RR [95%-CI]; p-value	0.12 [0.01, 0.97], 0.0463		2.95 [0.15, 57.00], 0.4740		0.43 [0.12, 1.53], 0.1926	
OR [95%-CI]; p-value	0.10 [0.01, 0.91], 0.0151		3.05 [0.15, 63.00], 0.4483		0.41 [0.11, 1.58], 0.1805	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.01], 0.0394		0.03 [-0.04, 0.11], 0.3695		-0.05 [-0.12, 0.03], 0.2306	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_3_m_pt_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.3.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.1779		0.7032		0.6951	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	3/59 (5.1)	3/29 (10.3)	1/59 (1.7)	1/31 (3.2)	4/118 (3.4)	4/60 (6.7)
RR [95%-CI]; p-value	0.49 [0.11, 2.29], 0.3652		0.53 [0.03, 8.12], 0.6450		0.51 [0.13, 1.96], 0.3264	
OR [95%-CI]; p-value	0.46 [0.09, 2.46], 0.3575		0.52 [0.03, 8.56], 0.6397		0.49 [0.12, 2.04], 0.3185	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4065		-0.02 [-0.09, 0.06], 0.6699		-0.03 [-0.10, 0.04], 0.3661	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	1/33 (3.0)	3/60 (5.0)	5/29 (17.2)	8/116 (6.9)	6/62 (9.7)
RR [95%-CI]; p-value	2.95 [0.36, 24.15], 0.3140		0.29 [0.07, 1.13], 0.0746		0.71 [0.26, 1.96], 0.5120	
OR [95%-CI]; p-value	3.14 [0.35, 28.09], 0.2838		0.25 [0.06, 1.14], 0.0584		0.69 [0.23, 2.09], 0.5114	
RD [95%-CI]; p-value	0.06 [-0.04, 0.15], 0.2230		-0.12 [-0.27, 0.03], 0.1053		-0.03 [-0.11, 0.06], 0.5303	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_3_m_pt_ae10pct_sex_pp.sas using SAS 9.4

Table 12.4.8.1.1.s2.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8112		0.7543		0.9754	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	1/59 (1.7)	0/29 (0.0)	0/59 (0.0)	1/31 (3.2)	1/118 (0.8)	1/60 (1.7)
RR [95%-CI]; p-value	1.00 [0.03, 28.96], 1.0000		0.26 [0.01, 7.55], 0.4336		0.51 [0.03, 7.99], 0.6303	
OR [95%-CI]; p-value	1.00 [0.03, 30.69], 1.0000		0.25 [0.01, 7.80], 0.3989		0.50 [0.03, 8.21], 0.6240	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 1.0000		-0.02 [-0.09, 0.04], 0.4812		-0.01 [-0.04, 0.03], 0.6589	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	1/33 (3.0)	2/60 (3.3)	2/29 (6.9)	3/116 (2.6)	3/62 (4.8)
RR [95%-CI]; p-value	0.59 [0.04, 9.11], 0.7050		0.48 [0.07, 3.26], 0.4554		0.53 [0.11, 2.57], 0.4343	
OR [95%-CI]; p-value	0.58 [0.04, 9.62], 0.7020		0.47 [0.06, 3.48], 0.4470		0.52 [0.10, 2.67], 0.4276	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.06], 0.7198		-0.04 [-0.14, 0.07], 0.4969		-0.02 [-0.08, 0.04], 0.4672	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_8_1_1_m_soc_sae5pct_sex_pp.sas using SAS 9.4

Table 12.4.8.1.2.s2.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_8_1_2_m_pt_sae5pct_sex_pp.sas using SAS 9.4

Table 12.4.5.1.1.s2.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_5_1_1_m_soc_aeg35pct_sex_pp.sas using SAS 9.4

Table 12.4.5.1.2.s2.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_5_1_2_m_pt_aeg35pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.8363		0.6883		0.9003	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	10/29 (34.5)	13/59 (22.0)	3/31 (9.7)	25/118 (21.2)	13/60 (21.7)
RR [95%-CI]; p-value	0.59 [0.29, 1.20], 0.1461		2.28 [0.70, 7.39], 0.1709		0.98 [0.54, 1.77], 0.9410	
OR [95%-CI]; p-value	0.49 [0.18, 1.31], 0.1498		2.64 [0.69, 10.08], 0.1451		0.97 [0.46, 2.07], 0.9411	
RD [95%-CI]; p-value	-0.14 [-0.34, 0.06], 0.1682		0.12 [-0.02, 0.27], 0.1026		-0.00 [-0.13, 0.12], 0.9412	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	8/33 (24.2)	10/60 (16.7)	3/29 (10.3)	19/116 (16.4)	11/62 (17.7)
RR [95%-CI]; p-value	0.66 [0.28, 1.55], 0.3430		1.61 [0.48, 5.41], 0.4404		0.92 [0.47, 1.81], 0.8166	
OR [95%-CI]; p-value	0.60 [0.21, 1.74], 0.3435		1.73 [0.44, 6.85], 0.4287		0.91 [0.40, 2.05], 0.8170	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.09], 0.3602		0.06 [-0.08, 0.21], 0.3945		-0.01 [-0.13, 0.10], 0.8187	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8968		0.2880		0.4617	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	8/59 (13.6)	7/29 (24.1)	7/59 (11.9)	2/31 (6.5)	15/118 (12.7)	9/60 (15.0)
RR [95%-CI]; p-value	0.56 [0.23, 1.40], 0.2151		1.84 [0.41, 8.33], 0.4291		0.85 [0.39, 1.82], 0.6718	
OR [95%-CI]; p-value	0.49 [0.16, 1.53], 0.2148		1.95 [0.38, 10.02], 0.4160		0.83 [0.34, 2.01], 0.6726	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2456		0.05 [-0.07, 0.17], 0.3748		-0.02 [-0.13, 0.09], 0.6794	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	7/56 (12.5)	8/33 (24.2)	7/60 (11.7)	5/29 (17.2)	14/116 (12.1)	13/62 (21.0)
RR [95%-CI]; p-value	0.52 [0.21, 1.29], 0.1576		0.68 [0.23, 1.95], 0.4696		0.58 [0.29, 1.15], 0.1162	
OR [95%-CI]; p-value	0.45 [0.15, 1.37], 0.1529		0.63 [0.18, 2.20], 0.4705		0.52 [0.23, 1.18], 0.1148	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1757		-0.06 [-0.22, 0.10], 0.4938		-0.09 [-0.21, 0.03], 0.1374	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.1251		0.8903		0.2081	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	22/59 (37.3)	8/29 (27.6)	18/59 (30.5)	9/31 (29.0)	40/118 (33.9)	17/60 (28.3)
RR [95%-CI]; p-value	1.35 [0.69, 2.66], 0.3824		1.05 [0.54, 2.06], 0.8849		1.20 [0.74, 1.92], 0.4591	
OR [95%-CI]; p-value	1.56 [0.59, 4.12], 0.3668		1.07 [0.41, 2.78], 0.8845		1.30 [0.66, 2.56], 0.4519	
RD [95%-CI]; p-value	0.10 [-0.11, 0.30], 0.3517		0.01 [-0.18, 0.21], 0.8840		0.06 [-0.09, 0.20], 0.4439	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	9/56 (16.1)	9/33 (27.3)	10/60 (16.7)	5/29 (17.2)	19/116 (16.4)	14/62 (22.6)
RR [95%-CI]; p-value	0.59 [0.26, 1.33], 0.2049		0.97 [0.36, 2.57], 0.9458		0.73 [0.39, 1.35], 0.3083	
OR [95%-CI]; p-value	0.51 [0.18, 1.45], 0.2038		0.96 [0.30, 3.12], 0.9459		0.67 [0.31, 1.45], 0.3104	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2222		-0.01 [-0.17, 0.16], 0.9461		-0.06 [-0.19, 0.06], 0.3269	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.6998		0.4383		0.3536	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	3/29 (10.3)	4/59 (6.8)	2/31 (6.5)	10/118 (8.5)	5/60 (8.3)
RR [95%-CI]; p-value	0.98 [0.26, 3.65], 0.9796		1.05 [0.20, 5.42], 0.9528		1.02 [0.36, 2.84], 0.9744	
OR [95%-CI]; p-value	0.98 [0.23, 4.24], 0.9796		1.05 [0.18, 6.10], 0.9527		1.02 [0.33, 3.13], 0.9744	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9797		0.00 [-0.10, 0.11], 0.9524		0.00 [-0.08, 0.09], 0.9744	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	2/33 (6.1)	4/60 (6.7)	0/29 (0.0)	9/116 (7.8)	2/62 (3.2)
RR [95%-CI]; p-value	1.47 [0.30, 7.17], 0.6313		3.93 [0.21, 71.97], 0.3558		2.41 [0.54, 10.79], 0.2518	
OR [95%-CI]; p-value	1.52 [0.28, 8.31], 0.6273		4.14 [0.21, 81.07], 0.3116		2.52 [0.53, 12.06], 0.2315	
RD [95%-CI]; p-value	0.03 [-0.08, 0.14], 0.6109		0.05 [-0.03, 0.13], 0.2142		0.05 [-0.02, 0.11], 0.1757	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.0634		0.7700		0.1043	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	10/59 (16.9)	3/29 (10.3)	5/59 (8.5)	2/31 (6.5)	15/118 (12.7)	5/60 (8.3)
RR [95%-CI]; p-value	1.64 [0.49, 5.50], 0.4243		1.31 [0.27, 6.38], 0.7353		1.53 [0.58, 4.00], 0.3902	
OR [95%-CI]; p-value	1.77 [0.45, 7.00], 0.4118		1.34 [0.25, 7.35], 0.7335		1.60 [0.55, 4.64], 0.3819	
RD [95%-CI]; p-value	0.07 [-0.08, 0.21], 0.3768		0.02 [-0.09, 0.13], 0.7232		0.04 [-0.05, 0.14], 0.3520	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	4/56 (7.1)	7/33 (21.2)	6/60 (10.0)	3/29 (10.3)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.34 [0.11, 1.06], 0.0637		0.97 [0.26, 3.59], 0.9596		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.29 [0.08, 1.06], 0.0514		0.96 [0.22, 4.16], 0.9597		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.14 [-0.30, 0.01], 0.0751		-0.00 [-0.14, 0.13], 0.9599		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0352		0.2680		0.3792	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	15/59 (25.4)	6/29 (20.7)	8/59 (13.6)	7/31 (22.6)	23/118 (19.5)	13/60 (21.7)
RR [95%-CI]; p-value	1.23 [0.53, 2.83], 0.6290		0.60 [0.24, 1.50], 0.2754		0.90 [0.49, 1.65], 0.7318	
OR [95%-CI]; p-value	1.31 [0.45, 3.82], 0.6243		0.54 [0.17, 1.66], 0.2752		0.88 [0.41, 1.88], 0.7327	
RD [95%-CI]; p-value	0.05 [-0.14, 0.23], 0.6152		-0.09 [-0.26, 0.08], 0.3016		-0.02 [-0.15, 0.10], 0.7359	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	13/33 (39.4)	13/60 (21.7)	5/29 (17.2)	21/116 (18.1)	18/62 (29.0)
RR [95%-CI]; p-value	0.36 [0.17, 0.78], 0.0097		1.26 [0.50, 3.19], 0.6306		0.62 [0.36, 1.08], 0.0917	
OR [95%-CI]; p-value	0.26 [0.09, 0.71], 0.0070		1.33 [0.42, 4.16], 0.6262		0.54 [0.26, 1.11], 0.0931	
RD [95%-CI]; p-value	-0.25 [-0.44, -0.06], 0.0097		0.04 [-0.13, 0.22], 0.6152		-0.11 [-0.24, 0.02], 0.1071	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.9665		0.0630		0.1769	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	12/59 (20.3)	11/29 (37.9)	14/59 (23.7)	6/31 (19.4)	26/118 (22.0)	17/60 (28.3)
RR [95%-CI]; p-value	0.54 [0.27, 1.07], 0.0753		1.23 [0.52, 2.87], 0.6392		0.78 [0.46, 1.32], 0.3492	
OR [95%-CI]; p-value	0.42 [0.16, 1.12], 0.0775		1.30 [0.44, 3.79], 0.6353		0.71 [0.35, 1.45], 0.3533	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.03], 0.0915		0.04 [-0.13, 0.22], 0.6270		-0.06 [-0.20, 0.07], 0.3652	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	9/33 (27.3)	6/60 (10.0)	8/29 (27.6)	14/116 (12.1)	17/62 (27.4)
RR [95%-CI]; p-value	0.52 [0.22, 1.23], 0.1358		0.36 [0.14, 0.95], 0.0385		0.44 [0.23, 0.83], 0.0115	
OR [95%-CI]; p-value	0.44 [0.15, 1.30], 0.1322		0.29 [0.09, 0.94], 0.0327		0.36 [0.16, 0.80], 0.0101	
RD [95%-CI]; p-value	-0.13 [-0.31, 0.05], 0.1514		-0.18 [-0.36, 0.00], 0.0548		-0.15 [-0.28, -0.03], 0.0168	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8198		0.3494		0.6250	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	6/29 (20.7)	8/59 (13.6)	3/31 (9.7)	14/118 (11.9)	9/60 (15.0)
RR [95%-CI]; p-value	0.49 [0.17, 1.39], 0.1810		1.40 [0.40, 4.91], 0.5980		0.79 [0.36, 1.72], 0.5545	
OR [95%-CI]; p-value	0.43 [0.13, 1.49], 0.1765		1.46 [0.36, 5.97], 0.5932		0.76 [0.31, 1.88], 0.5555	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.06], 0.2153		0.04 [-0.10, 0.17], 0.5755		-0.03 [-0.14, 0.08], 0.5677	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	5/33 (15.2)	5/60 (8.3)	4/29 (13.8)	10/116 (8.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.59 [0.18, 1.88], 0.3726		0.60 [0.18, 2.08], 0.4249		0.59 [0.25, 1.38], 0.2274	
OR [95%-CI]; p-value	0.55 [0.15, 2.06], 0.3692		0.57 [0.14, 2.30], 0.4233		0.56 [0.21, 1.45], 0.2249	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.08], 0.3948		-0.05 [-0.20, 0.09], 0.4564		-0.06 [-0.16, 0.04], 0.2548	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.6761		0.2140		0.5381	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	7/59 (11.9)	5/29 (17.2)	9/59 (15.3)	2/31 (6.5)	16/118 (13.6)	7/60 (11.7)
RR [95%-CI]; p-value	0.69 [0.24, 1.98], 0.4887		2.36 [0.54, 10.28], 0.2510		1.16 [0.51, 2.67], 0.7232	
OR [95%-CI]; p-value	0.65 [0.19, 2.24], 0.4896		2.61 [0.53, 12.91], 0.2257		1.19 [0.46, 3.07], 0.7220	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5110		0.09 [-0.04, 0.21], 0.1712		0.02 [-0.08, 0.12], 0.7162	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	8/56 (14.3)	5/33 (15.2)	4/60 (6.7)	3/29 (10.3)	12/116 (10.3)	8/62 (12.9)
RR [95%-CI]; p-value	0.94 [0.34, 2.64], 0.9110		0.64 [0.15, 2.69], 0.5470		0.80 [0.35, 1.86], 0.6060	
OR [95%-CI]; p-value	0.93 [0.28, 3.13], 0.9111		0.62 [0.13, 2.97], 0.5457		0.78 [0.30, 2.02], 0.6066	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9116		-0.04 [-0.16, 0.09], 0.5719		-0.03 [-0.13, 0.07], 0.6167	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3473		0.0953		0.0572	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	4/59 (6.8)	3/29 (10.3)	6/59 (10.2)	0/31 (0.0)	10/118 (8.5)	3/60 (5.0)
RR [95%-CI]; p-value	0.66 [0.16, 2.74], 0.5623		6.41 [0.37, 111.02], 0.2019		1.69 [0.48, 5.93], 0.4089	
OR [95%-CI]; p-value	0.63 [0.13, 3.02], 0.5613		7.02 [0.38, 129.99], 0.1320		1.76 [0.47, 6.65], 0.3997	
RD [95%-CI]; p-value	-0.04 [-0.16, 0.09], 0.5853		0.09 [-0.00, 0.17], 0.0577		0.03 [-0.04, 0.11], 0.3614	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	5/33 (15.2)	6/60 (10.0)	6/29 (20.7)	8/116 (6.9)	11/62 (17.7)
RR [95%-CI]; p-value	0.24 [0.05, 1.15], 0.0735		0.48 [0.17, 1.37], 0.1711		0.39 [0.16, 0.92], 0.0307	
OR [95%-CI]; p-value	0.21 [0.04, 1.14], 0.0500		0.43 [0.12, 1.46], 0.1664		0.34 [0.13, 0.91], 0.0256	
RD [95%-CI]; p-value	-0.12 [-0.25, 0.02], 0.0847		-0.11 [-0.27, 0.06], 0.2064		-0.11 [-0.21, -0.00], 0.0443	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.2.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8323		0.3804		0.5422	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	6/59 (10.2)	4/29 (13.8)	2/59 (3.4)	1/31 (3.2)	8/118 (6.8)	5/60 (8.3)
RR [95%-CI]; p-value	0.74 [0.23, 2.41], 0.6140		1.05 [0.10, 11.14], 0.9672		0.81 [0.28, 2.38], 0.7063	
OR [95%-CI]; p-value	0.71 [0.18, 2.73], 0.6146		1.05 [0.09, 12.09], 0.9671		0.80 [0.25, 2.56], 0.7065	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6297		0.00 [-0.08, 0.08], 0.9669		-0.02 [-0.10, 0.07], 0.7149	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	6/56 (10.7)	4/33 (12.1)	4/60 (6.7)	6/29 (20.7)	10/116 (8.6)	10/62 (16.1)
RR [95%-CI]; p-value	0.88 [0.27, 2.90], 0.8389		0.32 [0.10, 1.05], 0.0610		0.53 [0.24, 1.21], 0.1345	
OR [95%-CI]; p-value	0.87 [0.23, 3.34], 0.8391		0.27 [0.07, 1.06], 0.0496		0.49 [0.19, 1.25], 0.1307	
RD [95%-CI]; p-value	-0.01 [-0.15, 0.12], 0.8413		-0.14 [-0.30, 0.02], 0.0866		-0.08 [-0.18, 0.03], 0.1604	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_2_m_soc_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.4.s2.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.4387		0.9692		0.3829	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	8/29 (27.6)	3/59 (5.1)	0/31 (0.0)	5/118 (4.2)	8/60 (13.3)
RR [95%-CI]; p-value	0.12 [0.03, 0.54], 0.0056		3.20 [0.17, 61.97], 0.4412		0.32 [0.11, 0.93], 0.0363	
OR [95%-CI]; p-value	0.09 [0.02, 0.47], 0.0008		3.32 [0.16, 68.46], 0.4111		0.29 [0.09, 0.92], 0.0275	
RD [95%-CI]; p-value	-0.24 [-0.41, -0.07], 0.0050		0.03 [-0.04, 0.11], 0.3346		-0.09 [-0.18, 0.00], 0.0562	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	4/33 (12.1)	3/60 (5.0)	0/29 (0.0)	5/116 (4.3)	4/62 (6.5)
RR [95%-CI]; p-value	0.29 [0.06, 1.52], 0.1447		2.95 [0.15, 57.00], 0.4740		0.67 [0.19, 2.40], 0.5363	
OR [95%-CI]; p-value	0.27 [0.05, 1.56], 0.1202		3.05 [0.15, 63.00], 0.4483		0.65 [0.17, 2.53], 0.5345	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.04], 0.1678		0.03 [-0.04, 0.11], 0.3695		-0.02 [-0.09, 0.05], 0.5570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_4_m_pt_ae1pct_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.4039		0.6794		0.2180	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	9/59 (15.3)	1/29 (3.4)	3/59 (5.1)	2/31 (6.5)	12/118 (10.2)	3/60 (5.0)
RR [95%-CI]; p-value	4.42 [0.59, 33.27], 0.1486		0.79 [0.14, 4.47], 0.7880		2.03 [0.60, 6.93], 0.2565	
OR [95%-CI]; p-value	5.04 [0.61, 41.87], 0.1009		0.78 [0.12, 4.91], 0.7879		2.15 [0.58, 7.94], 0.2405	
RD [95%-CI]; p-value	0.12 [0.00, 0.23], 0.0410		-0.01 [-0.12, 0.09], 0.7949		0.05 [-0.03, 0.13], 0.1914	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	1/33 (3.0)	3/60 (5.0)	3/29 (10.3)	5/116 (4.3)	4/62 (6.5)
RR [95%-CI]; p-value	1.18 [0.11, 12.50], 0.8915		0.48 [0.10, 2.25], 0.3541		0.67 [0.19, 2.40], 0.5363	
OR [95%-CI]; p-value	1.19 [0.10, 13.60], 0.8913		0.46 [0.09, 2.41], 0.3459		0.65 [0.17, 2.53], 0.5345	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8891		-0.05 [-0.18, 0.07], 0.3975		-0.02 [-0.09, 0.05], 0.5570	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7374		NA		0.7769	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	0/29 (0.0)	0/59 (0.0)	0/31 (0.0)	0/118 (0.0)	0/60 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	0/60 (0.0)	0/29 (0.0)	1/116 (0.9)	0/62 (0.0)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		NA		1.08 [0.04, 31.67], 0.9654	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		NA		1.08 [0.04, 32.59], 0.9654	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		NA		0.00 [-0.03, 0.03], 0.9650	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2454		0.6794		0.1512	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	9/59 (15.3)	1/29 (3.4)	3/59 (5.1)	2/31 (6.5)	12/118 (10.2)	3/60 (5.0)
RR [95%-CI]; p-value	4.42 [0.59, 33.27], 0.1486		0.79 [0.14, 4.47], 0.7880		2.03 [0.60, 6.93], 0.2565	
OR [95%-CI]; p-value	5.04 [0.61, 41.87], 0.1009		0.78 [0.12, 4.91], 0.7879		2.15 [0.58, 7.94], 0.2405	
RD [95%-CI]; p-value	0.12 [0.00, 0.23], 0.0410		-0.01 [-0.12, 0.09], 0.7949		0.05 [-0.03, 0.13], 0.1914	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	1/33 (3.0)	3/60 (5.0)	3/29 (10.3)	4/116 (3.4)	4/62 (6.5)
RR [95%-CI]; p-value	0.59 [0.04, 9.11], 0.7050		0.48 [0.10, 2.25], 0.3541		0.53 [0.14, 2.06], 0.3635	
OR [95%-CI]; p-value	0.58 [0.04, 9.62], 0.7020		0.46 [0.09, 2.41], 0.3459		0.52 [0.12, 2.15], 0.3568	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.06], 0.7198		-0.05 [-0.18, 0.07], 0.3975		-0.03 [-0.10, 0.04], 0.3976	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8074		0.8137		0.9760	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	4/59 (6.8)	1/29 (3.4)	0/59 (0.0)	0/31 (0.0)	4/118 (3.4)	1/60 (1.7)
RR [95%-CI]; p-value	1.97 [0.23, 16.81], 0.5369		NA		2.03 [0.23, 17.80], 0.5212	
OR [95%-CI]; p-value	2.04 [0.22, 19.09], 0.5257		NA		2.07 [0.23, 18.94], 0.5107	
RD [95%-CI]; p-value	0.03 [-0.06, 0.13], 0.4795		NA		0.02 [-0.03, 0.06], 0.4628	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	1/60 (1.7)	0/29 (0.0)	2/116 (1.7)	0/62 (0.0)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		0.98 [0.03, 28.48], 0.9922		2.16 [0.10, 47.07], 0.6255	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		0.98 [0.03, 30.16], 0.9922		2.18 [0.10, 48.99], 0.6162	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		-0.00 [-0.06, 0.06], 0.9922		0.01 [-0.02, 0.04], 0.5760	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.5673		0.8069		0.5291	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	5/59 (8.5)	3/29 (10.3)	4/59 (6.8)	2/31 (6.5)	9/118 (7.6)	5/60 (8.3)
RR [95%-CI]; p-value	0.82 [0.21, 3.19], 0.7739		1.05 [0.20, 5.42], 0.9528		0.92 [0.32, 2.61], 0.8685	
OR [95%-CI]; p-value	0.80 [0.18, 3.62], 0.7742		1.05 [0.18, 6.10], 0.9527		0.91 [0.29, 2.84], 0.8686	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.11], 0.7807		0.00 [-0.10, 0.11], 0.9524		-0.01 [-0.09, 0.08], 0.8703	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	5/56 (8.9)	6/33 (18.2)	5/60 (8.3)	3/29 (10.3)	10/116 (8.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.49 [0.16, 1.48], 0.2076		0.81 [0.21, 3.14], 0.7555		0.59 [0.25, 1.38], 0.2274	
OR [95%-CI]; p-value	0.44 [0.12, 1.58], 0.2001		0.79 [0.17, 3.55], 0.7558		0.56 [0.21, 1.45], 0.2249	
RD [95%-CI]; p-value	-0.09 [-0.24, 0.06], 0.2307		-0.02 [-0.15, 0.11], 0.7636		-0.06 [-0.16, 0.04], 0.2548	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.7374		0.7203		0.9843	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	0/59 (0.0)	0/29 (0.0)	1/59 (1.7)	0/31 (0.0)	1/118 (0.8)	0/60 (0.0)
RR [95%-CI]; p-value	NA		1.07 [0.04, 30.96], 0.9695		1.03 [0.03, 30.13], 0.9884	
OR [95%-CI]; p-value	NA		1.07 [0.03, 32.76], 0.9695		1.03 [0.03, 31.01], 0.9884	
RD [95%-CI]; p-value	NA		0.00 [-0.05, 0.06], 0.9692		0.00 [-0.03, 0.03], 0.9883	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	1/56 (1.8)	0/33 (0.0)	1/60 (1.7)	1/29 (3.4)	2/116 (1.7)	1/62 (1.6)
RR [95%-CI]; p-value	1.20 [0.04, 34.71], 0.9169		0.48 [0.03, 7.46], 0.6025		1.07 [0.10, 11.56], 0.9562	
OR [95%-CI]; p-value	1.20 [0.04, 36.76], 0.9167		0.47 [0.03, 7.87], 0.5951		1.07 [0.10, 12.04], 0.9562	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9149		-0.02 [-0.09, 0.06], 0.6365		0.00 [-0.04, 0.04], 0.9558	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
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Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.4255		0.9845		0.5514	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	5/59 (8.5)	3/29 (10.3)	3/59 (5.1)	2/31 (6.5)	8/118 (6.8)	5/60 (8.3)
RR [95%-CI]; p-value	0.82 [0.21, 3.19], 0.7739		0.79 [0.14, 4.47], 0.7880		0.81 [0.28, 2.38], 0.7063	
OR [95%-CI]; p-value	0.80 [0.18, 3.62], 0.7742		0.78 [0.12, 4.91], 0.7879		0.80 [0.25, 2.56], 0.7065	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.11], 0.7807		-0.01 [-0.12, 0.09], 0.7949		-0.02 [-0.10, 0.07], 0.7149	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	4/56 (7.1)	6/33 (18.2)	5/60 (8.3)	3/29 (10.3)	9/116 (7.8)	9/62 (14.5)
RR [95%-CI]; p-value	0.39 [0.12, 1.29], 0.1238		0.81 [0.21, 3.14], 0.7555		0.53 [0.22, 1.28], 0.1586	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1112		0.79 [0.17, 3.55], 0.7558		0.50 [0.19, 1.32], 0.1542	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1434		-0.02 [-0.15, 0.11], 0.7636		-0.07 [-0.17, 0.03], 0.1866	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.7.s2.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9354		0.9622		0.8465	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	2/59 (3.4)	0/29 (0.0)	1/59 (1.7)	0/31 (0.0)	3/118 (2.5)	0/60 (0.0)
RR [95%-CI]; p-value	2.00 [0.09, 42.97], 0.6578		1.07 [0.04, 30.96], 0.9695		3.08 [0.16, 60.43], 0.4595	
OR [95%-CI]; p-value	2.04 [0.09, 46.60], 0.6501		1.07 [0.03, 32.76], 0.9695		3.13 [0.15, 63.52], 0.4338	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.6125		0.00 [-0.05, 0.06], 0.9692		0.02 [-0.02, 0.05], 0.3559	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	2/56 (3.6)	0/33 (0.0)	2/60 (3.3)	1/29 (3.4)	4/116 (3.4)	1/62 (1.6)
RR [95%-CI]; p-value	2.39 [0.11, 51.51], 0.5774		0.97 [0.09, 10.23], 0.9775		2.14 [0.24, 18.72], 0.4924	
OR [95%-CI]; p-value	2.44 [0.11, 55.86], 0.5635		0.97 [0.08, 11.10], 0.9775		2.18 [0.24, 19.93], 0.4801	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5219		-0.00 [-0.08, 0.08], 0.9777		0.02 [-0.03, 0.06], 0.4309	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_7_m_pt_smq_sex_pp.sas using SAS 9.4

Table 12.4.4.1.6.s2.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Female vs 2.Male

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.4035		0.8851		0.3977	
1.Female	N1=59	N1=29	N1=59	N1=31	N1=118	N1=60
n/N1 (%)	9/59 (15.3)	11/29 (37.9)	12/59 (20.3)	4/31 (12.9)	21/118 (17.8)	15/60 (25.0)
RR [95%-CI]; p-value	0.40 [0.19, 0.86], 0.0189		1.58 [0.55, 4.48], 0.3933		0.71 [0.40, 1.28], 0.2550	
OR [95%-CI]; p-value	0.29 [0.10, 0.83], 0.0170		1.72 [0.51, 5.88], 0.3806		0.65 [0.31, 1.38], 0.2580	
RD [95%-CI]; p-value	-0.23 [-0.43, -0.03], 0.0255		0.07 [-0.08, 0.23], 0.3516		-0.07 [-0.20, 0.06], 0.2756	
2.Male	N2=56	N2=33	N2=60	N2=29	N2=116	N2=62
n/N2 (%)	7/56 (12.5)	6/33 (18.2)	11/60 (18.3)	3/29 (10.3)	18/116 (15.5)	9/62 (14.5)
RR [95%-CI]; p-value	0.69 [0.25, 1.87], 0.4636		1.77 [0.54, 5.87], 0.3488		1.07 [0.51, 2.24], 0.8595	
OR [95%-CI]; p-value	0.64 [0.20, 2.11], 0.4635		1.95 [0.50, 7.60], 0.3320		1.08 [0.45, 2.57], 0.8592	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.10], 0.4796		0.08 [-0.07, 0.23], 0.2897		0.01 [-0.10, 0.12], 0.8580	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no responder in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk>1, Odds Ratio>1 and Risk Difference>0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s2_sex_pp/T12_4_4_1_6_m_pt_adr_sex_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.6162		0.6120		0.5834	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	40/58 (69.0)	22/30 (73.3)	35/60 (58.3)	13/24 (54.2)	75/118 (63.6)	35/54 (64.8)
RR [95%-CI]; p-value	0.94 [0.71, 1.24], 0.6632		1.08 [0.70, 1.65], 0.7329		0.98 [0.77, 1.25], 0.8727	
OR [95%-CI]; p-value	0.81 [0.30, 2.16], 0.6703		1.18 [0.46, 3.07], 0.7274		0.95 [0.48, 1.86], 0.8735	
RD [95%-CI]; p-value	-0.04 [-0.24, 0.15], 0.6655		0.04 [-0.19, 0.28], 0.7284		-0.01 [-0.17, 0.14], 0.8732	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	43/57 (75.4)	28/32 (87.5)	37/59 (62.7)	24/36 (66.7)	80/116 (69.0)	52/68 (76.5)
RR [95%-CI]; p-value	0.86 [0.71, 1.05], 0.1415		0.94 [0.69, 1.27], 0.6928		0.90 [0.75, 1.08], 0.2598	
OR [95%-CI]; p-value	0.44 [0.13, 1.47], 0.1740		0.84 [0.35, 2.01], 0.6965		0.68 [0.34, 1.36], 0.2751	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.04], 0.1397		-0.04 [-0.24, 0.16], 0.6945		-0.08 [-0.21, 0.06], 0.2628	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.9827		0.3106		0.3638	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	6/30 (20.0)	7/60 (11.7)	2/24 (8.3)	15/118 (12.7)	8/54 (14.8)
RR [95%-CI]; p-value	0.69 [0.26, 1.81], 0.4492		1.40 [0.31, 6.26], 0.6599		0.86 [0.39, 1.90], 0.7060	
OR [95%-CI]; p-value	0.64 [0.20, 2.05], 0.4505		1.45 [0.28, 7.55], 0.6554		0.84 [0.33, 2.11], 0.7069	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4701		0.03 [-0.10, 0.17], 0.6340		-0.02 [-0.13, 0.09], 0.7134	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	4/32 (12.5)	6/59 (10.2)	0/36 (0.0)	11/116 (9.5)	4/68 (5.9)
RR [95%-CI]; p-value	0.70 [0.20, 2.43], 0.5761		7.42 [0.43, 129.02], 0.1688		1.61 [0.53, 4.86], 0.3968	
OR [95%-CI]; p-value	0.67 [0.17, 2.71], 0.5756		8.15 [0.44, 150.51], 0.0971		1.68 [0.51, 5.49], 0.3890	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.10], 0.5914		0.09 [0.00, 0.17], 0.0445		0.04 [-0.04, 0.11], 0.3611	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.3457		0.6541		0.6014	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	6/58 (10.3)	3/30 (10.0)	0/60 (0.0)	1/24 (4.2)	6/118 (5.1)	4/54 (7.4)
RR [95%-CI]; p-value	1.03 [0.28, 3.85], 0.9597		0.20 [0.01, 5.72], 0.3456		0.69 [0.20, 2.33], 0.5467	
OR [95%-CI]; p-value	1.04 [0.24, 4.48], 0.9596		0.19 [0.01, 5.91], 0.2944		0.67 [0.18, 2.48], 0.5458	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9594		-0.03 [-0.12, 0.05], 0.4310		-0.02 [-0.10, 0.06], 0.5708	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	1/32 (3.1)	3/59 (5.1)	4/36 (11.1)	9/116 (7.8)	5/68 (7.4)
RR [95%-CI]; p-value	3.37 [0.42, 26.75], 0.2507		0.46 [0.11, 1.93], 0.2868		1.06 [0.37, 3.02], 0.9203	
OR [95%-CI]; p-value	3.65 [0.42, 31.74], 0.2132		0.43 [0.09, 2.04], 0.2754		1.06 [0.34, 3.30], 0.9202	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1465		-0.06 [-0.18, 0.06], 0.3126		0.00 [-0.07, 0.08], 0.9197	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.6380		0.3837		0.3868	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	3/30 (10.0)	5/60 (8.3)	1/24 (4.2)	13/118 (11.0)	4/54 (7.4)
RR [95%-CI]; p-value	1.38 [0.39, 4.82], 0.6145		2.00 [0.25, 16.24], 0.5165		1.49 [0.51, 4.35], 0.4686	
OR [95%-CI]; p-value	1.44 [0.35, 5.88], 0.6101		2.09 [0.23, 18.90], 0.5029		1.55 [0.48, 4.99], 0.4616	
RD [95%-CI]; p-value	0.04 [-0.10, 0.18], 0.5935		0.04 [-0.06, 0.15], 0.4420		0.04 [-0.05, 0.13], 0.4310	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	12/57 (21.1)	7/32 (21.9)	7/59 (11.9)	6/36 (16.7)	19/116 (16.4)	13/68 (19.1)
RR [95%-CI]; p-value	0.96 [0.42, 2.20], 0.9275		0.71 [0.26, 1.95], 0.5090		0.86 [0.45, 1.62], 0.6353	
OR [95%-CI]; p-value	0.95 [0.33, 2.73], 0.9276		0.67 [0.21, 2.19], 0.5088		0.83 [0.38, 1.81], 0.6362	
RD [95%-CI]; p-value	-0.01 [-0.19, 0.17], 0.9279		-0.05 [-0.20, 0.10], 0.5222		-0.03 [-0.14, 0.09], 0.6413	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.9425		0.9963		0.8261	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	1/30 (3.3)	3/60 (5.0)	0/24 (0.0)	6/118 (5.1)	1/54 (1.9)
RR [95%-CI]; p-value	1.55 [0.17, 14.28], 0.6981		2.45 [0.13, 47.13], 0.5525		2.75 [0.34, 22.25], 0.3441	
OR [95%-CI]; p-value	1.58 [0.16, 15.90], 0.6946		2.53 [0.12, 52.37], 0.5356		2.84 [0.33, 24.18], 0.3193	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6747		0.03 [-0.05, 0.11], 0.4605		0.03 [-0.02, 0.09], 0.2364	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	2/32 (6.3)	2/59 (3.4)	0/36 (0.0)	7/116 (6.0)	2/68 (2.9)
RR [95%-CI]; p-value	1.40 [0.29, 6.83], 0.6744		2.47 [0.11, 53.38], 0.5631		2.05 [0.44, 9.60], 0.3612	
OR [95%-CI]; p-value	1.44 [0.26, 7.90], 0.6715		2.53 [0.11, 57.61], 0.5480		2.12 [0.43, 10.51], 0.3477	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6575		0.02 [-0.04, 0.08], 0.5066		0.03 [-0.03, 0.09], 0.3048	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.5390		NA		0.4999	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	0/58 (0.0)	1/30 (3.3)	0/60 (0.0)	0/24 (0.0)	0/118 (0.0)	1/54 (1.9)
RR [95%-CI]; p-value	0.26 [0.01, 7.43], 0.4281		NA		0.23 [0.01, 6.69], 0.3910	
OR [95%-CI]; p-value	0.25 [0.01, 7.67], 0.3925		NA		0.22 [0.01, 6.80], 0.3482	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.04], 0.4777		NA		-0.01 [-0.05, 0.02], 0.4585	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	1/116 (0.9)	0/68 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.07], 0.9391		NA		1.18 [0.04, 34.74], 0.9232	
OR [95%-CI]; p-value	1.14 [0.04, 35.02], 0.9390		NA		1.18 [0.04, 35.72], 0.9231	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9379		NA		0.00 [-0.02, 0.03], 0.9214	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7635		NA		0.7191	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	0/58 (0.0)	1/30 (3.3)	0/60 (0.0)	0/24 (0.0)	0/118 (0.0)	1/54 (1.9)
RR [95%-CI]; p-value	0.26 [0.01, 7.43], 0.4281		NA		0.23 [0.01, 6.69], 0.3910	
OR [95%-CI]; p-value	0.25 [0.01, 7.67], 0.3925		NA		0.22 [0.01, 6.80], 0.3482	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.04], 0.4777		NA		-0.01 [-0.05, 0.02], 0.4585	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	0/57 (0.0)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	0/116 (0.0)	0/68 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.6171		0.1494		0.2338	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	35/58 (60.3)	21/30 (70.0)	32/60 (53.3)	9/24 (37.5)	67/118 (56.8)	30/54 (55.6)
RR [95%-CI]; p-value	0.86 [0.63, 1.18], 0.3538		1.42 [0.81, 2.51], 0.2243		1.02 [0.77, 1.36], 0.8812	
OR [95%-CI]; p-value	0.65 [0.25, 1.67], 0.3721		1.90 [0.72, 5.02], 0.1897		1.05 [0.55, 2.01], 0.8806	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3600		0.16 [-0.07, 0.39], 0.1795		0.01 [-0.15, 0.17], 0.8807	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	33/57 (57.9)	24/32 (75.0)	28/59 (47.5)	20/36 (55.6)	61/116 (52.6)	44/68 (64.7)
RR [95%-CI]; p-value	0.77 [0.57, 1.04], 0.0891		0.85 [0.57, 1.27], 0.4365		0.81 [0.64, 1.04], 0.0989	
OR [95%-CI]; p-value	0.46 [0.18, 1.19], 0.1066		0.72 [0.31, 1.66], 0.4438		0.60 [0.33, 1.12], 0.1089	
RD [95%-CI]; p-value	-0.17 [-0.37, 0.03], 0.0893		-0.08 [-0.29, 0.13], 0.4418		-0.12 [-0.27, 0.02], 0.1025	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.5192		0.7978		0.4793	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	15/58 (25.9)	11/30 (36.7)	16/60 (26.7)	6/24 (25.0)	31/118 (26.3)	17/54 (31.5)
RR [95%-CI]; p-value	0.71 [0.37, 1.34], 0.2859		1.07 [0.47, 2.40], 0.8759		0.83 [0.51, 1.37], 0.4748	
OR [95%-CI]; p-value	0.60 [0.23, 1.55], 0.2923		1.09 [0.37, 3.23], 0.8753		0.78 [0.38, 1.57], 0.4796	
RD [95%-CI]; p-value	-0.11 [-0.31, 0.10], 0.3039		0.02 [-0.19, 0.22], 0.8741		-0.05 [-0.20, 0.10], 0.4877	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	23/57 (40.4)	14/32 (43.8)	20/59 (33.9)	10/36 (27.8)	43/116 (37.1)	24/68 (35.3)
RR [95%-CI]; p-value	0.92 [0.56, 1.53], 0.7531		1.22 [0.65, 2.30], 0.5394		1.05 [0.70, 1.57], 0.8099	
OR [95%-CI]; p-value	0.87 [0.36, 2.09], 0.7549		1.33 [0.54, 3.30], 0.5335		1.08 [0.58, 2.02], 0.8092	
RD [95%-CI]; p-value	-0.03 [-0.25, 0.18], 0.7555		0.06 [-0.13, 0.25], 0.5272		0.02 [-0.13, 0.16], 0.8086	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s3.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.3457		0.6541		0.6014	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	6/58 (10.3)	3/30 (10.0)	0/60 (0.0)	1/24 (4.2)	6/118 (5.1)	4/54 (7.4)
RR [95%-CI]; p-value	1.03 [0.28, 3.85], 0.9597		0.20 [0.01, 5.72], 0.3456		0.69 [0.20, 2.33], 0.5467	
OR [95%-CI]; p-value	1.04 [0.24, 4.48], 0.9596		0.19 [0.01, 5.91], 0.2944		0.67 [0.18, 2.48], 0.5458	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9594		-0.03 [-0.12, 0.05], 0.4310		-0.02 [-0.10, 0.06], 0.5708	
2.Baseline Weight ≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	1/32 (3.1)	3/59 (5.1)	4/36 (11.1)	9/116 (7.8)	5/68 (7.4)
RR [95%-CI]; p-value	3.37 [0.42, 26.75], 0.2507		0.46 [0.11, 1.93], 0.2868		1.06 [0.37, 3.02], 0.9203	
OR [95%-CI]; p-value	3.65 [0.42, 31.74], 0.2132		0.43 [0.09, 2.04], 0.2754		1.06 [0.34, 3.30], 0.9202	
RD [95%-CI]; p-value	0.07 [-0.03, 0.17], 0.1465		-0.06 [-0.18, 0.06], 0.3126		0.00 [-0.07, 0.08], 0.9197	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_3_1_m_sf_ttl_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.9173		0.6521		0.9055	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	3/30 (10.0)	3/60 (5.0)	1/24 (4.2)	6/118 (5.1)	4/54 (7.4)
RR [95%-CI]; p-value	0.52 [0.11, 2.41], 0.4010		1.20 [0.13, 10.97], 0.8717		0.69 [0.20, 2.33], 0.5467	
OR [95%-CI]; p-value	0.49 [0.09, 2.60], 0.3944		1.21 [0.12, 12.25], 0.8713		0.67 [0.18, 2.48], 0.5458	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.07], 0.4363		0.01 [-0.09, 0.11], 0.8664		-0.02 [-0.10, 0.06], 0.5708	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	6/32 (18.8)	4/59 (6.8)	1/36 (2.8)	9/116 (7.8)	7/68 (10.3)
RR [95%-CI]; p-value	0.47 [0.15, 1.41], 0.1779		2.44 [0.28, 20.99], 0.4164		0.75 [0.29, 1.93], 0.5560	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1699		2.55 [0.27, 23.72], 0.3968		0.73 [0.26, 2.07], 0.5557	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.2038		0.04 [-0.04, 0.12], 0.3484		-0.03 [-0.11, 0.06], 0.5683	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4484		0.3292		0.4487	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	8/30 (26.7)	11/60 (18.3)	1/24 (4.2)	23/118 (19.5)	9/54 (16.7)
RR [95%-CI]; p-value	0.78 [0.36, 1.69], 0.5229		4.40 [0.60, 32.24], 0.1448		1.17 [0.58, 2.36], 0.6612	
OR [95%-CI]; p-value	0.72 [0.26, 2.01], 0.5259		5.16 [0.63, 42.43], 0.0937		1.21 [0.52, 2.83], 0.6586	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5364		0.14 [0.02, 0.27], 0.0280		0.03 [-0.09, 0.15], 0.6511	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	9/57 (15.8)	10/32 (31.3)	12/59 (20.3)	5/36 (13.9)	21/116 (18.1)	15/68 (22.1)
RR [95%-CI]; p-value	0.51 [0.23, 1.11], 0.0902		1.46 [0.56, 3.81], 0.4349		0.82 [0.45, 1.48], 0.5123	
OR [95%-CI]; p-value	0.41 [0.15, 1.16], 0.0876		1.58 [0.51, 4.94], 0.4262		0.78 [0.37, 1.64], 0.5139	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.03], 0.1041		0.06 [-0.09, 0.22], 0.4077		-0.04 [-0.16, 0.08], 0.5215	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.9013		0.9216		0.6662	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	7/30 (23.3)	5/60 (8.3)	2/24 (8.3)	12/118 (10.2)	9/54 (16.7)
RR [95%-CI]; p-value	0.52 [0.20, 1.34], 0.1740		1.00 [0.21, 4.81], 1.0000		0.61 [0.27, 1.36], 0.2273	
OR [95%-CI]; p-value	0.45 [0.14, 1.44], 0.1709		1.00 [0.18, 5.54], 1.0000		0.57 [0.22, 1.44], 0.2271	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.06], 0.2019		0.00 [-0.13, 0.13], 1.0000		-0.06 [-0.18, 0.05], 0.2614	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	8/32 (25.0)	9/59 (15.3)	5/36 (13.9)	17/116 (14.7)	13/68 (19.1)
RR [95%-CI]; p-value	0.56 [0.23, 1.35], 0.1981		1.10 [0.40, 3.02], 0.8558		0.77 [0.40, 1.48], 0.4279	
OR [95%-CI]; p-value	0.49 [0.16, 1.46], 0.1961		1.12 [0.34, 3.64], 0.8555		0.73 [0.33, 1.61], 0.4290	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2195		0.01 [-0.13, 0.16], 0.8541		-0.04 [-0.16, 0.07], 0.4409	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.5158		0.8373		0.7787	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	16/58 (27.6)	7/30 (23.3)	12/60 (20.0)	5/24 (20.8)	28/118 (23.7)	12/54 (22.2)
RR [95%-CI]; p-value	1.18 [0.55, 2.56], 0.6704		0.96 [0.38, 2.43], 0.9314		1.07 [0.59, 1.94], 0.8288	
OR [95%-CI]; p-value	1.25 [0.45, 3.48], 0.6669		0.95 [0.29, 3.06], 0.9316		1.09 [0.50, 2.35], 0.8282	
RD [95%-CI]; p-value	0.04 [-0.15, 0.23], 0.6610		-0.01 [-0.20, 0.18], 0.9320		0.02 [-0.12, 0.15], 0.8267	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	15/57 (26.3)	10/32 (31.3)	16/59 (27.1)	9/36 (25.0)	31/116 (26.7)	19/68 (27.9)
RR [95%-CI]; p-value	0.84 [0.43, 1.65], 0.6167		1.08 [0.54, 2.19], 0.8207		0.96 [0.59, 1.56], 0.8576	
OR [95%-CI]; p-value	0.79 [0.30, 2.04], 0.6192		1.12 [0.43, 2.88], 0.8200		0.94 [0.48, 1.84], 0.8578	
RD [95%-CI]; p-value	-0.05 [-0.25, 0.15], 0.6237		0.02 [-0.16, 0.20], 0.8189		-0.01 [-0.15, 0.12], 0.8583	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2503		0.6085		0.2470	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	9/58 (15.5)	4/30 (13.3)	7/60 (11.7)	2/24 (8.3)	16/118 (13.6)	6/54 (11.1)
RR [95%-CI]; p-value	1.16 [0.39, 3.47], 0.7855		1.40 [0.31, 6.26], 0.6599		1.22 [0.51, 2.95], 0.6579	
OR [95%-CI]; p-value	1.19 [0.34, 4.25], 0.7843		1.45 [0.28, 7.55], 0.6554		1.25 [0.46, 3.41], 0.6555	
RD [95%-CI]; p-value	0.02 [-0.13, 0.18], 0.7800		0.03 [-0.10, 0.17], 0.6340		0.02 [-0.08, 0.13], 0.6449	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	6/32 (18.8)	4/59 (6.8)	3/36 (8.3)	9/116 (7.8)	9/68 (13.2)
RR [95%-CI]; p-value	0.47 [0.15, 1.41], 0.1779		0.81 [0.19, 3.43], 0.7786		0.59 [0.24, 1.40], 0.2311	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1699		0.80 [0.17, 3.80], 0.7786		0.55 [0.21, 1.46], 0.2274	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.2038		-0.02 [-0.13, 0.10], 0.7834		-0.05 [-0.15, 0.04], 0.2541	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5948		0.7957		0.7736	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	13/58 (22.4)	9/30 (30.0)	8/60 (13.3)	3/24 (12.5)	21/118 (17.8)	12/54 (22.2)
RR [95%-CI]; p-value	0.75 [0.36, 1.55], 0.4317		1.07 [0.31, 3.68], 0.9187		0.80 [0.43, 1.51], 0.4910	
OR [95%-CI]; p-value	0.67 [0.25, 1.82], 0.4360		1.08 [0.26, 4.46], 0.9185		0.76 [0.34, 1.68], 0.4939	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.12], 0.4480		0.01 [-0.15, 0.17], 0.9176		-0.04 [-0.17, 0.09], 0.5066	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	10/57 (17.5)	10/32 (31.3)	13/59 (22.0)	9/36 (25.0)	23/116 (19.8)	19/68 (27.9)
RR [95%-CI]; p-value	0.56 [0.26, 1.20], 0.1376		0.88 [0.42, 1.85], 0.7387		0.71 [0.42, 1.20], 0.2036	
OR [95%-CI]; p-value	0.47 [0.17, 1.29], 0.1371		0.85 [0.32, 2.24], 0.7395		0.64 [0.32, 1.28], 0.2056	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1542		-0.03 [-0.21, 0.15], 0.7420		-0.08 [-0.21, 0.05], 0.2176	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3472		0.0175		0.0219	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	9/30 (30.0)	13/60 (21.7)	2/24 (8.3)	25/118 (21.2)	11/54 (20.4)
RR [95%-CI]; p-value	0.69 [0.33, 1.45], 0.3273		2.60 [0.63, 10.66], 0.1846		1.04 [0.55, 1.96], 0.9030	
OR [95%-CI]; p-value	0.61 [0.22, 1.67], 0.3314		3.04 [0.63, 14.66], 0.1495		1.05 [0.47, 2.33], 0.9028	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.10], 0.3477		0.13 [-0.02, 0.29], 0.0855		0.01 [-0.12, 0.14], 0.9023	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	11/32 (34.4)	7/59 (11.9)	12/36 (33.3)	15/116 (12.9)	23/68 (33.8)
RR [95%-CI]; p-value	0.41 [0.18, 0.91], 0.0284		0.36 [0.15, 0.82], 0.0153		0.38 [0.21, 0.68], 0.0011	
OR [95%-CI]; p-value	0.31 [0.11, 0.89], 0.0246		0.27 [0.09, 0.77], 0.0112		0.29 [0.14, 0.61], 0.0007	
RD [95%-CI]; p-value	-0.20 [-0.39, -0.02], 0.0336		-0.21 [-0.39, -0.04], 0.0160		-0.21 [-0.34, -0.08], 0.0014	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.9180		0.1935		0.4617	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	5/58 (8.6)	5/30 (16.7)	7/60 (11.7)	1/24 (4.2)	12/118 (10.2)	6/54 (11.1)
RR [95%-CI]; p-value	0.52 [0.16, 1.65], 0.2647		2.80 [0.36, 21.56], 0.3228		0.92 [0.36, 2.31], 0.8513	
OR [95%-CI]; p-value	0.47 [0.13, 1.78], 0.2596		3.04 [0.35, 26.12], 0.2901		0.91 [0.32, 2.56], 0.8515	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2984		0.08 [-0.04, 0.19], 0.1971		-0.01 [-0.11, 0.09], 0.8536	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	6/32 (18.8)	6/59 (10.2)	6/36 (16.7)	12/116 (10.3)	12/68 (17.6)
RR [95%-CI]; p-value	0.56 [0.20, 1.60], 0.2791		0.61 [0.21, 1.75], 0.3578		0.59 [0.28, 1.23], 0.1583	
OR [95%-CI]; p-value	0.51 [0.15, 1.74], 0.2757		0.57 [0.17, 1.91], 0.3551		0.54 [0.23, 1.28], 0.1557	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.3045		-0.06 [-0.21, 0.08], 0.3769		-0.07 [-0.18, 0.03], 0.1778	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.5887		0.7473		0.8294	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	4/30 (13.3)	2/60 (3.3)	0/24 (0.0)	5/118 (4.2)	4/54 (7.4)
RR [95%-CI]; p-value	0.39 [0.09, 1.62], 0.1945		1.63 [0.08, 34.94], 0.7536		0.57 [0.16, 2.05], 0.3904	
OR [95%-CI]; p-value	0.35 [0.07, 1.70], 0.1799		1.66 [0.07, 38.06], 0.7504		0.55 [0.14, 2.15], 0.3862	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2338		0.01 [-0.06, 0.09], 0.7253		-0.03 [-0.11, 0.05], 0.4301	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	3/32 (9.4)	3/59 (5.1)	2/36 (5.6)	4/116 (3.4)	5/68 (7.4)
RR [95%-CI]; p-value	0.19 [0.02, 1.73], 0.1392		0.92 [0.16, 5.22], 0.9206		0.47 [0.13, 1.69], 0.2464	
OR [95%-CI]; p-value	0.17 [0.02, 1.73], 0.0959		0.91 [0.14, 5.73], 0.9206		0.45 [0.12, 1.74], 0.2359	
RD [95%-CI]; p-value	-0.08 [-0.18, 0.03], 0.1611		-0.00 [-0.10, 0.09], 0.9214		-0.04 [-0.11, 0.03], 0.2768	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4170		0.8929		0.5255	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	6/30 (20.0)	7/60 (11.7)	2/24 (8.3)	14/118 (11.9)	8/54 (14.8)
RR [95%-CI]; p-value	0.60 [0.22, 1.64], 0.3209		1.40 [0.31, 6.26], 0.6599		0.80 [0.36, 1.79], 0.5895	
OR [95%-CI]; p-value	0.55 [0.17, 1.81], 0.3203		1.45 [0.28, 7.55], 0.6554		0.77 [0.30, 1.97], 0.5908	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3487		0.03 [-0.10, 0.17], 0.6340		-0.03 [-0.14, 0.08], 0.6033	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	4/32 (12.5)	6/59 (10.2)	3/36 (8.3)	14/116 (12.1)	7/68 (10.3)
RR [95%-CI]; p-value	1.12 [0.37, 3.44], 0.8393		1.22 [0.33, 4.58], 0.7679		1.17 [0.50, 2.76], 0.7159	
OR [95%-CI]; p-value	1.14 [0.32, 4.14], 0.8388		1.25 [0.29, 5.32], 0.7669		1.20 [0.46, 3.13], 0.7148	
RD [95%-CI]; p-value	0.02 [-0.13, 0.16], 0.8365		0.02 [-0.10, 0.14], 0.7618		0.02 [-0.08, 0.11], 0.7097	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0990		0.3403		0.0226	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	0/30 (0.0)	8/60 (13.3)	2/24 (8.3)	11/118 (9.3)	2/54 (3.7)
RR [95%-CI]; p-value	3.16 [0.16, 60.99], 0.4470		1.60 [0.37, 7.00], 0.5324		2.52 [0.58, 10.97], 0.2190	
OR [95%-CI]; p-value	3.27 [0.16, 67.52], 0.4177		1.69 [0.33, 8.62], 0.5227		2.67 [0.57, 12.50], 0.1958	
RD [95%-CI]; p-value	0.04 [-0.04, 0.11], 0.3406		0.05 [-0.09, 0.19], 0.4842		0.06 [-0.02, 0.13], 0.1300	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	8/32 (25.0)	4/59 (6.8)	4/36 (11.1)	7/116 (6.0)	12/68 (17.6)
RR [95%-CI]; p-value	0.21 [0.06, 0.74], 0.0149		0.61 [0.16, 2.29], 0.4641		0.34 [0.14, 0.83], 0.0172	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0066		0.58 [0.14, 2.49], 0.4608		0.30 [0.11, 0.80], 0.0125	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0162		-0.04 [-0.16, 0.08], 0.4831		-0.12 [-0.22, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.1.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7689		0.6603		0.9926	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	3/30 (10.0)	3/60 (5.0)	2/24 (8.3)	7/118 (5.9)	5/54 (9.3)
RR [95%-CI]; p-value	0.69 [0.16, 2.88], 0.6107		0.60 [0.11, 3.37], 0.5617		0.64 [0.21, 1.93], 0.4282	
OR [95%-CI]; p-value	0.67 [0.14, 3.19], 0.6101		0.58 [0.09, 3.70], 0.5597		0.62 [0.19, 2.04], 0.4267	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6282		-0.03 [-0.16, 0.09], 0.5970		-0.03 [-0.12, 0.06], 0.4601	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	5/32 (15.6)	3/59 (5.1)	5/36 (13.9)	11/116 (9.5)	10/68 (14.7)
RR [95%-CI]; p-value	0.90 [0.32, 2.52], 0.8382		0.37 [0.09, 1.44], 0.1506		0.64 [0.29, 1.44], 0.2838	
OR [95%-CI]; p-value	0.88 [0.26, 2.96], 0.8385		0.33 [0.07, 1.48], 0.1339		0.61 [0.24, 1.52], 0.2821	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8404		-0.09 [-0.21, 0.04], 0.1712		-0.05 [-0.15, 0.05], 0.3042	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_1_m_soc_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.3.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3457		0.8458		0.4349	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	6/30 (20.0)	3/60 (5.0)	0/24 (0.0)	4/118 (3.4)	6/54 (11.1)
RR [95%-CI]; p-value	0.09 [0.01, 0.68], 0.0203		2.45 [0.13, 47.13], 0.5525		0.31 [0.09, 1.04], 0.0572	
OR [95%-CI]; p-value	0.07 [0.01, 0.61], 0.0027		2.53 [0.12, 52.37], 0.5356		0.28 [0.08, 1.04], 0.0446	
RD [95%-CI]; p-value	-0.18 [-0.33, -0.04], 0.0148		0.03 [-0.05, 0.11], 0.4605		-0.08 [-0.17, 0.01], 0.0925	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	6/32 (18.8)	3/59 (5.1)	0/36 (0.0)	6/116 (5.2)	6/68 (8.8)
RR [95%-CI]; p-value	0.28 [0.08, 1.05], 0.0586		3.71 [0.19, 72.01], 0.3860		0.59 [0.20, 1.75], 0.3374	
OR [95%-CI]; p-value	0.24 [0.06, 1.04], 0.0429		3.86 [0.19, 79.28], 0.3478		0.56 [0.17, 1.82], 0.3329	
RD [95%-CI]; p-value	-0.13 [-0.28, 0.01], 0.0724		0.04 [-0.03, 0.10], 0.2812		-0.04 [-0.12, 0.04], 0.3622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_3_m_pt_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.3.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.1244		0.9690		0.3797	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	3/30 (10.0)	2/60 (3.3)	0/24 (0.0)	6/118 (5.1)	3/54 (5.6)
RR [95%-CI]; p-value	0.69 [0.16, 2.88], 0.6107		1.63 [0.08, 34.94], 0.7536		0.92 [0.24, 3.52], 0.8975	
OR [95%-CI]; p-value	0.67 [0.14, 3.19], 0.6101		1.66 [0.07, 38.06], 0.7504		0.91 [0.22, 3.79], 0.8976	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6282		0.01 [-0.06, 0.09], 0.7253		-0.00 [-0.08, 0.07], 0.8992	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	0/57 (0.0)	5/32 (15.6)	5/59 (8.5)	2/36 (5.6)	5/116 (4.3)	7/68 (10.3)
RR [95%-CI]; p-value	0.06 [0.00, 0.99], 0.0489		1.53 [0.31, 7.45], 0.6019		0.42 [0.14, 1.27], 0.1235	
OR [95%-CI]; p-value	0.05 [0.00, 0.90], 0.0053		1.57 [0.29, 8.57], 0.5973		0.39 [0.12, 1.29], 0.1126	
RD [95%-CI]; p-value	-0.15 [-0.28, -0.02], 0.0239		0.03 [-0.07, 0.13], 0.5793		-0.06 [-0.14, 0.02], 0.1483	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_3_m_pt_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.3.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.9526		0.4123		0.6475	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	2/58 (3.4)	1/30 (3.3)	2/60 (3.3)	1/24 (4.2)	4/118 (3.4)	2/54 (3.7)
RR [95%-CI]; p-value	1.03 [0.10, 10.95], 0.9775		0.80 [0.08, 8.42], 0.8526		0.92 [0.17, 4.85], 0.9171	
OR [95%-CI]; p-value	1.04 [0.09, 11.91], 0.9775		0.79 [0.07, 9.18], 0.8525		0.91 [0.16, 5.14], 0.9171	
RD [95%-CI]; p-value	0.00 [-0.08, 0.08], 0.9774		-0.01 [-0.10, 0.08], 0.8590		-0.00 [-0.06, 0.06], 0.9184	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	3/32 (9.4)	2/59 (3.4)	5/36 (13.9)	8/116 (6.9)	8/68 (11.8)
RR [95%-CI]; p-value	1.12 [0.30, 4.19], 0.8631		0.24 [0.05, 1.19], 0.0815		0.59 [0.23, 1.49], 0.2620	
OR [95%-CI]; p-value	1.14 [0.26, 4.89], 0.8627		0.22 [0.04, 1.19], 0.0574		0.56 [0.20, 1.56], 0.2580	
RD [95%-CI]; p-value	0.01 [-0.12, 0.14], 0.8607		-0.10 [-0.23, 0.02], 0.0918		-0.05 [-0.14, 0.04], 0.2858	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_3_m_pt_ae10pct_wt_pp.sas using SAS 9.4

Table 12.4.8.1.1.s3.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.7768		0.4992		0.3034	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	0/30 (0.0)	1/60 (1.7)	0/24 (0.0)	2/118 (1.7)	0/54 (0.0)
RR [95%-CI]; p-value	1.05 [0.04, 30.47], 0.9766		0.82 [0.03, 23.56], 0.9060		1.85 [0.08, 40.29], 0.6963	
OR [95%-CI]; p-value	1.05 [0.03, 32.29], 0.9766		0.81 [0.03, 25.06], 0.9059		1.86 [0.08, 41.99], 0.6912	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9764		-0.00 [-0.07, 0.06], 0.9097		0.01 [-0.03, 0.04], 0.6578	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	1/32 (3.1)	1/59 (1.7)	3/36 (8.3)	2/116 (1.7)	4/68 (5.9)
RR [95%-CI]; p-value	0.56 [0.04, 8.68], 0.6794		0.20 [0.02, 1.88], 0.1606		0.29 [0.06, 1.56], 0.1500	
OR [95%-CI]; p-value	0.55 [0.03, 9.16], 0.6755		0.19 [0.02, 1.90], 0.1181		0.28 [0.05, 1.58], 0.1253	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.06], 0.6981		-0.07 [-0.16, 0.03], 0.1758		-0.04 [-0.10, 0.02], 0.1796	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_8_1_1_m_soc_sae5pct_wt_pp.sas using SAS 9.4

Table 12.4.8.1.2.s3.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_8_1_2_m_pt_sae5pct_wt_pp.sas using SAS 9.4

Table 12.4.5.1.1.s3.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_5_1_1_m_soc_aeg35pct_wt_pp.sas using SAS 9.4

Table 12.4.5.1.2.s3.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_5_1_2_m_pt_aeg35pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4484		0.3292		0.4487	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	8/30 (26.7)	11/60 (18.3)	1/24 (4.2)	23/118 (19.5)	9/54 (16.7)
RR [95%-CI]; p-value	0.78 [0.36, 1.69], 0.5229		4.40 [0.60, 32.24], 0.1448		1.17 [0.58, 2.36], 0.6612	
OR [95%-CI]; p-value	0.72 [0.26, 2.01], 0.5259		5.16 [0.63, 42.43], 0.0937		1.21 [0.52, 2.83], 0.6586	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5364		0.14 [0.02, 0.27], 0.0280		0.03 [-0.09, 0.15], 0.6511	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	9/57 (15.8)	10/32 (31.3)	12/59 (20.3)	5/36 (13.9)	21/116 (18.1)	15/68 (22.1)
RR [95%-CI]; p-value	0.51 [0.23, 1.11], 0.0902		1.46 [0.56, 3.81], 0.4349		0.82 [0.45, 1.48], 0.5123	
OR [95%-CI]; p-value	0.41 [0.15, 1.16], 0.0876		1.58 [0.51, 4.94], 0.4262		0.78 [0.37, 1.64], 0.5139	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.03], 0.1041		0.06 [-0.09, 0.22], 0.4077		-0.04 [-0.16, 0.08], 0.5215	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.9013		0.9216		0.6662	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	7/30 (23.3)	5/60 (8.3)	2/24 (8.3)	12/118 (10.2)	9/54 (16.7)
RR [95%-CI]; p-value	0.52 [0.20, 1.34], 0.1740		1.00 [0.21, 4.81], 1.0000		0.61 [0.27, 1.36], 0.2273	
OR [95%-CI]; p-value	0.45 [0.14, 1.44], 0.1709		1.00 [0.18, 5.54], 1.0000		0.57 [0.22, 1.44], 0.2271	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.06], 0.2019		0.00 [-0.13, 0.13], 1.0000		-0.06 [-0.18, 0.05], 0.2614	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	8/32 (25.0)	9/59 (15.3)	5/36 (13.9)	17/116 (14.7)	13/68 (19.1)
RR [95%-CI]; p-value	0.56 [0.23, 1.35], 0.1981		1.10 [0.40, 3.02], 0.8558		0.77 [0.40, 1.48], 0.4279	
OR [95%-CI]; p-value	0.49 [0.16, 1.46], 0.1961		1.12 [0.34, 3.64], 0.8555		0.73 [0.33, 1.61], 0.4290	
RD [95%-CI]; p-value	-0.11 [-0.28, 0.07], 0.2195		0.01 [-0.13, 0.16], 0.8541		-0.04 [-0.16, 0.07], 0.4409	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.5158		0.8373		0.7787	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	16/58 (27.6)	7/30 (23.3)	12/60 (20.0)	5/24 (20.8)	28/118 (23.7)	12/54 (22.2)
RR [95%-CI]; p-value	1.18 [0.55, 2.56], 0.6704		0.96 [0.38, 2.43], 0.9314		1.07 [0.59, 1.94], 0.8288	
OR [95%-CI]; p-value	1.25 [0.45, 3.48], 0.6669		0.95 [0.29, 3.06], 0.9316		1.09 [0.50, 2.35], 0.8282	
RD [95%-CI]; p-value	0.04 [-0.15, 0.23], 0.6610		-0.01 [-0.20, 0.18], 0.9320		0.02 [-0.12, 0.15], 0.8267	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	15/57 (26.3)	10/32 (31.3)	16/59 (27.1)	9/36 (25.0)	31/116 (26.7)	19/68 (27.9)
RR [95%-CI]; p-value	0.84 [0.43, 1.65], 0.6167		1.08 [0.54, 2.19], 0.8207		0.96 [0.59, 1.56], 0.8576	
OR [95%-CI]; p-value	0.79 [0.30, 2.04], 0.6192		1.12 [0.43, 2.88], 0.8200		0.94 [0.48, 1.84], 0.8578	
RD [95%-CI]; p-value	-0.05 [-0.25, 0.15], 0.6237		0.02 [-0.16, 0.20], 0.8189		-0.01 [-0.15, 0.12], 0.8583	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.7712		0.7850		0.6182	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	6/58 (10.3)	3/30 (10.0)	4/60 (6.7)	1/24 (4.2)	10/118 (8.5)	4/54 (7.4)
RR [95%-CI]; p-value	1.03 [0.28, 3.85], 0.9597		1.60 [0.19, 13.59], 0.6668		1.14 [0.38, 3.49], 0.8128	
OR [95%-CI]; p-value	1.04 [0.24, 4.48], 0.9596		1.64 [0.17, 15.50], 0.6618		1.16 [0.35, 3.87], 0.8122	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9594		0.03 [-0.08, 0.13], 0.6305		0.01 [-0.08, 0.10], 0.8079	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	2/32 (6.3)	4/59 (6.8)	1/36 (2.8)	9/116 (7.8)	3/68 (4.4)
RR [95%-CI]; p-value	1.40 [0.29, 6.83], 0.6744		2.44 [0.28, 20.99], 0.4164		1.76 [0.49, 6.27], 0.3843	
OR [95%-CI]; p-value	1.44 [0.26, 7.90], 0.6715		2.55 [0.27, 23.72], 0.3968		1.82 [0.48, 6.98], 0.3748	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6575		0.04 [-0.04, 0.12], 0.3484		0.03 [-0.04, 0.10], 0.3413	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2503		0.6085		0.2470	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	9/58 (15.5)	4/30 (13.3)	7/60 (11.7)	2/24 (8.3)	16/118 (13.6)	6/54 (11.1)
RR [95%-CI]; p-value	1.16 [0.39, 3.47], 0.7855		1.40 [0.31, 6.26], 0.6599		1.22 [0.51, 2.95], 0.6579	
OR [95%-CI]; p-value	1.19 [0.34, 4.25], 0.7843		1.45 [0.28, 7.55], 0.6554		1.25 [0.46, 3.41], 0.6555	
RD [95%-CI]; p-value	0.02 [-0.13, 0.18], 0.7800		0.03 [-0.10, 0.17], 0.6340		0.02 [-0.08, 0.13], 0.6449	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	5/57 (8.8)	6/32 (18.8)	4/59 (6.8)	3/36 (8.3)	9/116 (7.8)	9/68 (13.2)
RR [95%-CI]; p-value	0.47 [0.15, 1.41], 0.1779		0.81 [0.19, 3.43], 0.7786		0.59 [0.24, 1.40], 0.2311	
OR [95%-CI]; p-value	0.42 [0.12, 1.49], 0.1699		0.80 [0.17, 3.80], 0.7786		0.55 [0.21, 1.46], 0.2274	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.2038		-0.02 [-0.13, 0.10], 0.7834		-0.05 [-0.15, 0.04], 0.2541	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5948		0.7957		0.7736	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	13/58 (22.4)	9/30 (30.0)	8/60 (13.3)	3/24 (12.5)	21/118 (17.8)	12/54 (22.2)
RR [95%-CI]; p-value	0.75 [0.36, 1.55], 0.4317		1.07 [0.31, 3.68], 0.9187		0.80 [0.43, 1.51], 0.4910	
OR [95%-CI]; p-value	0.67 [0.25, 1.82], 0.4360		1.08 [0.26, 4.46], 0.9185		0.76 [0.34, 1.68], 0.4939	
RD [95%-CI]; p-value	-0.08 [-0.27, 0.12], 0.4480		0.01 [-0.15, 0.17], 0.9176		-0.04 [-0.17, 0.09], 0.5066	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	10/57 (17.5)	10/32 (31.3)	13/59 (22.0)	9/36 (25.0)	23/116 (19.8)	19/68 (27.9)
RR [95%-CI]; p-value	0.56 [0.26, 1.20], 0.1376		0.88 [0.42, 1.85], 0.7387		0.71 [0.42, 1.20], 0.2036	
OR [95%-CI]; p-value	0.47 [0.17, 1.29], 0.1371		0.85 [0.32, 2.24], 0.7395		0.64 [0.32, 1.28], 0.2056	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1542		-0.03 [-0.21, 0.15], 0.7420		-0.08 [-0.21, 0.05], 0.2176	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.3472		0.0175		0.0219	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	12/58 (20.7)	9/30 (30.0)	13/60 (21.7)	2/24 (8.3)	25/118 (21.2)	11/54 (20.4)
RR [95%-CI]; p-value	0.69 [0.33, 1.45], 0.3273		2.60 [0.63, 10.66], 0.1846		1.04 [0.55, 1.96], 0.9030	
OR [95%-CI]; p-value	0.61 [0.22, 1.67], 0.3314		3.04 [0.63, 14.66], 0.1495		1.05 [0.47, 2.33], 0.9028	
RD [95%-CI]; p-value	-0.09 [-0.29, 0.10], 0.3477		0.13 [-0.02, 0.29], 0.0855		0.01 [-0.12, 0.14], 0.9023	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	11/32 (34.4)	7/59 (11.9)	12/36 (33.3)	15/116 (12.9)	23/68 (33.8)
RR [95%-CI]; p-value	0.41 [0.18, 0.91], 0.0284		0.36 [0.15, 0.82], 0.0153		0.38 [0.21, 0.68], 0.0011	
OR [95%-CI]; p-value	0.31 [0.11, 0.89], 0.0246		0.27 [0.09, 0.77], 0.0112		0.29 [0.14, 0.61], 0.0007	
RD [95%-CI]; p-value	-0.20 [-0.39, -0.02], 0.0336		-0.21 [-0.39, -0.04], 0.0160		-0.21 [-0.34, -0.08], 0.0014	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.9180		0.1935		0.4617	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	5/58 (8.6)	5/30 (16.7)	7/60 (11.7)	1/24 (4.2)	12/118 (10.2)	6/54 (11.1)
RR [95%-CI]; p-value	0.52 [0.16, 1.65], 0.2647		2.80 [0.36, 21.56], 0.3228		0.92 [0.36, 2.31], 0.8513	
OR [95%-CI]; p-value	0.47 [0.13, 1.78], 0.2596		3.04 [0.35, 26.12], 0.2901		0.91 [0.32, 2.56], 0.8515	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.2984		0.08 [-0.04, 0.19], 0.1971		-0.01 [-0.11, 0.09], 0.8536	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	6/32 (18.8)	6/59 (10.2)	6/36 (16.7)	12/116 (10.3)	12/68 (17.6)
RR [95%-CI]; p-value	0.56 [0.20, 1.60], 0.2791		0.61 [0.21, 1.75], 0.3578		0.59 [0.28, 1.23], 0.1583	
OR [95%-CI]; p-value	0.51 [0.15, 1.74], 0.2757		0.57 [0.17, 1.91], 0.3551		0.54 [0.23, 1.28], 0.1557	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.3045		-0.06 [-0.21, 0.08], 0.3769		-0.07 [-0.18, 0.03], 0.1778	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.4170		0.8929		0.5255	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	6/30 (20.0)	7/60 (11.7)	2/24 (8.3)	14/118 (11.9)	8/54 (14.8)
RR [95%-CI]; p-value	0.60 [0.22, 1.64], 0.3209		1.40 [0.31, 6.26], 0.6599		0.80 [0.36, 1.79], 0.5895	
OR [95%-CI]; p-value	0.55 [0.17, 1.81], 0.3203		1.45 [0.28, 7.55], 0.6554		0.77 [0.30, 1.97], 0.5908	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3487		0.03 [-0.10, 0.17], 0.6340		-0.03 [-0.14, 0.08], 0.6033	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	4/32 (12.5)	6/59 (10.2)	3/36 (8.3)	14/116 (12.1)	7/68 (10.3)
RR [95%-CI]; p-value	1.12 [0.37, 3.44], 0.8393		1.22 [0.33, 4.58], 0.7679		1.17 [0.50, 2.76], 0.7159	
OR [95%-CI]; p-value	1.14 [0.32, 4.14], 0.8388		1.25 [0.29, 5.32], 0.7669		1.20 [0.46, 3.13], 0.7148	
RD [95%-CI]; p-value	0.02 [-0.13, 0.16], 0.8365		0.02 [-0.10, 0.14], 0.7618		0.02 [-0.08, 0.11], 0.7097	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0990		0.3403		0.0226	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	0/30 (0.0)	8/60 (13.3)	2/24 (8.3)	11/118 (9.3)	2/54 (3.7)
RR [95%-CI]; p-value	3.16 [0.16, 60.99], 0.4470		1.60 [0.37, 7.00], 0.5324		2.52 [0.58, 10.97], 0.2190	
OR [95%-CI]; p-value	3.27 [0.16, 67.52], 0.4177		1.69 [0.33, 8.62], 0.5227		2.67 [0.57, 12.50], 0.1958	
RD [95%-CI]; p-value	0.04 [-0.04, 0.11], 0.3406		0.05 [-0.09, 0.19], 0.4842		0.06 [-0.02, 0.13], 0.1300	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	8/32 (25.0)	4/59 (6.8)	4/36 (11.1)	7/116 (6.0)	12/68 (17.6)
RR [95%-CI]; p-value	0.21 [0.06, 0.74], 0.0149		0.61 [0.16, 2.29], 0.4641		0.34 [0.14, 0.83], 0.0172	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0066		0.58 [0.14, 2.49], 0.4608		0.30 [0.11, 0.80], 0.0125	
RD [95%-CI]; p-value	-0.20 [-0.36, -0.04], 0.0162		-0.04 [-0.16, 0.08], 0.4831		-0.12 [-0.22, -0.02], 0.0234	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.2.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7689		0.6603		0.9926	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	3/30 (10.0)	3/60 (5.0)	2/24 (8.3)	7/118 (5.9)	5/54 (9.3)
RR [95%-CI]; p-value	0.69 [0.16, 2.88], 0.6107		0.60 [0.11, 3.37], 0.5617		0.64 [0.21, 1.93], 0.4282	
OR [95%-CI]; p-value	0.67 [0.14, 3.19], 0.6101		0.58 [0.09, 3.70], 0.5597		0.62 [0.19, 2.04], 0.4267	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6282		-0.03 [-0.16, 0.09], 0.5970		-0.03 [-0.12, 0.06], 0.4601	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	8/57 (14.0)	5/32 (15.6)	3/59 (5.1)	5/36 (13.9)	11/116 (9.5)	10/68 (14.7)
RR [95%-CI]; p-value	0.90 [0.32, 2.52], 0.8382		0.37 [0.09, 1.44], 0.1506		0.64 [0.29, 1.44], 0.2838	
OR [95%-CI]; p-value	0.88 [0.26, 2.96], 0.8385		0.33 [0.07, 1.48], 0.1339		0.61 [0.24, 1.52], 0.2821	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8404		-0.09 [-0.21, 0.04], 0.1712		-0.05 [-0.15, 0.05], 0.3042	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_2_m_soc_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.4.s3.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT

PP Population

Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.3457		0.8458		0.4349	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	6/30 (20.0)	3/60 (5.0)	0/24 (0.0)	4/118 (3.4)	6/54 (11.1)
RR [95%-CI]; p-value	0.09 [0.01, 0.68], 0.0203		2.45 [0.13, 47.13], 0.5525		0.31 [0.09, 1.04], 0.0572	
OR [95%-CI]; p-value	0.07 [0.01, 0.61], 0.0027		2.53 [0.12, 52.37], 0.5356		0.28 [0.08, 1.04], 0.0446	
RD [95%-CI]; p-value	-0.18 [-0.33, -0.04], 0.0148		0.03 [-0.05, 0.11], 0.4605		-0.08 [-0.17, 0.01], 0.0925	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	6/32 (18.8)	3/59 (5.1)	0/36 (0.0)	6/116 (5.2)	6/68 (8.8)
RR [95%-CI]; p-value	0.28 [0.08, 1.05], 0.0586		3.71 [0.19, 72.01], 0.3860		0.59 [0.20, 1.75], 0.3374	
OR [95%-CI]; p-value	0.24 [0.06, 1.04], 0.0429		3.86 [0.19, 79.28], 0.3478		0.56 [0.17, 1.82], 0.3329	
RD [95%-CI]; p-value	-0.13 [-0.28, 0.01], 0.0724		0.04 [-0.03, 0.10], 0.2812		-0.04 [-0.12, 0.04], 0.3622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_4_m_pt_ae1pct_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.7662		0.4741		0.4674	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	2/30 (6.7)	3/60 (5.0)	1/24 (4.2)	11/118 (9.3)	3/54 (5.6)
RR [95%-CI]; p-value	2.07 [0.47, 9.14], 0.3374		1.20 [0.13, 10.97], 0.8717		1.68 [0.49, 5.77], 0.4115	
OR [95%-CI]; p-value	2.24 [0.44, 11.29], 0.3180		1.21 [0.12, 12.25], 0.8713		1.75 [0.47, 6.54], 0.4018	
RD [95%-CI]; p-value	0.07 [-0.05, 0.20], 0.2671		0.01 [-0.09, 0.11], 0.8664		0.04 [-0.04, 0.12], 0.3593	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	3/57 (5.3)	0/32 (0.0)	3/59 (5.1)	4/36 (11.1)	6/116 (5.2)	4/68 (5.9)
RR [95%-CI]; p-value	3.42 [0.18, 66.20], 0.4158		0.46 [0.11, 1.93], 0.2868		0.88 [0.26, 3.01], 0.8375	
OR [95%-CI]; p-value	3.56 [0.17, 73.27], 0.3820		0.43 [0.09, 2.04], 0.2754		0.87 [0.24, 3.21], 0.8375	
RD [95%-CI]; p-value	0.04 [-0.03, 0.11], 0.3091		-0.06 [-0.18, 0.06], 0.3126		-0.01 [-0.08, 0.06], 0.8400	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7658		NA		0.7205	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	0/58 (0.0)	0/30 (0.0)	0/60 (0.0)	0/24 (0.0)	0/118 (0.0)	0/54 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	1/116 (0.9)	0/68 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.07], 0.9391		NA		1.18 [0.04, 34.74], 0.9232	
OR [95%-CI]; p-value	1.14 [0.04, 35.02], 0.9390		NA		1.18 [0.04, 35.72], 0.9231	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9379		NA		0.00 [-0.02, 0.03], 0.9214	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9553		0.4741		0.3614	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	8/58 (13.8)	2/30 (6.7)	3/60 (5.0)	1/24 (4.2)	11/118 (9.3)	3/54 (5.6)
RR [95%-CI]; p-value	2.07 [0.47, 9.14], 0.3374		1.20 [0.13, 10.97], 0.8717		1.68 [0.49, 5.77], 0.4115	
OR [95%-CI]; p-value	2.24 [0.44, 11.29], 0.3180		1.21 [0.12, 12.25], 0.8713		1.75 [0.47, 6.54], 0.4018	
RD [95%-CI]; p-value	0.07 [-0.05, 0.20], 0.2671		0.01 [-0.09, 0.11], 0.8664		0.04 [-0.04, 0.12], 0.3593	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	2/57 (3.5)	0/32 (0.0)	3/59 (5.1)	4/36 (11.1)	5/116 (4.3)	4/68 (5.9)
RR [95%-CI]; p-value	2.28 [0.11, 49.08], 0.5985		0.46 [0.11, 1.93], 0.2868		0.73 [0.20, 2.64], 0.6341	
OR [95%-CI]; p-value	2.33 [0.10, 53.21], 0.5864		0.43 [0.09, 2.04], 0.2754		0.72 [0.19, 2.78], 0.6332	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5451		-0.06 [-0.18, 0.06], 0.3126		-0.02 [-0.08, 0.05], 0.6458	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.7700		0.9132		0.7454	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	1/30 (3.3)	1/60 (1.7)	0/24 (0.0)	5/118 (4.2)	1/54 (1.9)
RR [95%-CI]; p-value	2.07 [0.24, 17.70], 0.5068		0.82 [0.03, 23.56], 0.9060		2.29 [0.27, 19.12], 0.4447	
OR [95%-CI]; p-value	2.15 [0.23, 20.12], 0.4937		0.81 [0.03, 25.06], 0.9059		2.35 [0.27, 20.57], 0.4288	
RD [95%-CI]; p-value	0.04 [-0.06, 0.13], 0.4455		-0.00 [-0.07, 0.06], 0.9097		0.02 [-0.03, 0.07], 0.3605	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	1/57 (1.8)	0/32 (0.0)	0/59 (0.0)	0/36 (0.0)	1/116 (0.9)	0/68 (0.0)
RR [95%-CI]; p-value	1.14 [0.04, 33.07], 0.9391		NA		1.18 [0.04, 34.74], 0.9232	
OR [95%-CI]; p-value	1.14 [0.04, 35.02], 0.9390		NA		1.18 [0.04, 35.72], 0.9231	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9379		NA		0.00 [-0.02, 0.03], 0.9214	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7629		0.1703		0.2469	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	4/58 (6.9)	4/30 (13.3)	3/60 (5.0)	3/24 (12.5)	7/118 (5.9)	7/54 (13.0)
RR [95%-CI]; p-value	0.52 [0.14, 1.92], 0.3254		0.40 [0.09, 1.84], 0.2401		0.46 [0.17, 1.24], 0.1243	
OR [95%-CI]; p-value	0.48 [0.11, 2.08], 0.3194		0.37 [0.07, 1.97], 0.2279		0.42 [0.14, 1.27], 0.1176	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.07], 0.3607		-0.08 [-0.22, 0.07], 0.3051		-0.07 [-0.17, 0.03], 0.1648	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	5/32 (15.6)	6/59 (10.2)	2/36 (5.6)	12/116 (10.3)	7/68 (10.3)
RR [95%-CI]; p-value	0.67 [0.22, 2.03], 0.4836		1.83 [0.39, 8.59], 0.4433		1.00 [0.42, 2.43], 0.9913	
OR [95%-CI]; p-value	0.64 [0.18, 2.27], 0.4831		1.92 [0.37, 10.09], 0.4321		1.01 [0.38, 2.69], 0.9913	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.10], 0.5022		0.05 [-0.06, 0.15], 0.4000		0.00 [-0.09, 0.09], 0.9913	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8131		0.2773		0.4365	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	1/58 (1.7)	0/30 (0.0)	0/60 (0.0)	1/24 (4.2)	1/118 (0.8)	1/54 (1.9)
RR [95%-CI]; p-value	1.05 [0.04, 30.47], 0.9766		0.20 [0.01, 5.72], 0.3456		0.46 [0.03, 7.18], 0.5779	
OR [95%-CI]; p-value	1.05 [0.03, 32.29], 0.9766		0.19 [0.01, 5.91], 0.2944		0.45 [0.03, 7.38], 0.5685	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9764		-0.03 [-0.12, 0.05], 0.4310		-0.01 [-0.05, 0.03], 0.6189	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	0/57 (0.0)	0/32 (0.0)	2/59 (3.4)	0/36 (0.0)	2/116 (1.7)	0/68 (0.0)
RR [95%-CI]; p-value	NA		2.47 [0.11, 53.38], 0.5631		2.36 [0.11, 51.63], 0.5850	
OR [95%-CI]; p-value	NA		2.53 [0.11, 57.61], 0.5480		2.39 [0.11, 53.68], 0.5725	
RD [95%-CI]; p-value	NA		0.02 [-0.04, 0.08], 0.5066		0.01 [-0.02, 0.04], 0.5310	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.5496		0.2337		0.2240	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	3/58 (5.2)	4/30 (13.3)	3/60 (5.0)	3/24 (12.5)	6/118 (5.1)	7/54 (13.0)
RR [95%-CI]; p-value	0.39 [0.09, 1.62], 0.1945		0.40 [0.09, 1.84], 0.2401		0.39 [0.14, 1.11], 0.0783	
OR [95%-CI]; p-value	0.35 [0.07, 1.70], 0.1799		0.37 [0.07, 1.97], 0.2279		0.36 [0.11, 1.13], 0.0697	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.05], 0.2338		-0.08 [-0.22, 0.07], 0.3051		-0.08 [-0.18, 0.02], 0.1150	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	6/57 (10.5)	5/32 (15.6)	5/59 (8.5)	2/36 (5.6)	11/116 (9.5)	7/68 (10.3)
RR [95%-CI]; p-value	0.67 [0.22, 2.03], 0.4836		1.53 [0.31, 7.45], 0.6019		0.92 [0.37, 2.26], 0.8580	
OR [95%-CI]; p-value	0.64 [0.18, 2.27], 0.4831		1.57 [0.29, 8.57], 0.5973		0.91 [0.34, 2.48], 0.8581	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.10], 0.5022		0.03 [-0.07, 0.13], 0.5793		-0.01 [-0.10, 0.08], 0.8594	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.7.s3.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9708		0.3848		0.5109	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	2/58 (3.4)	0/30 (0.0)	1/60 (1.7)	1/24 (4.2)	3/118 (2.5)	1/54 (1.9)
RR [95%-CI]; p-value	2.10 [0.10, 45.21], 0.6347		0.40 [0.03, 6.14], 0.5108		1.37 [0.15, 12.90], 0.7816	
OR [95%-CI]; p-value	2.14 [0.09, 49.04], 0.6255		0.39 [0.02, 6.50], 0.4972		1.38 [0.14, 13.60], 0.7803	
RD [95%-CI]; p-value	0.02 [-0.05, 0.08], 0.5859		-0.03 [-0.11, 0.06], 0.5700		0.01 [-0.04, 0.05], 0.7677	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	2/57 (3.5)	0/32 (0.0)	2/59 (3.4)	0/36 (0.0)	4/116 (3.4)	0/68 (0.0)
RR [95%-CI]; p-value	2.28 [0.11, 49.08], 0.5985		2.47 [0.11, 53.38], 0.5631		4.72 [0.25, 88.01], 0.2981	
OR [95%-CI]; p-value	2.33 [0.10, 53.21], 0.5864		2.53 [0.11, 57.61], 0.5480		4.86 [0.25, 93.30], 0.2475	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5451		0.02 [-0.04, 0.08], 0.5066		0.03 [-0.01, 0.07], 0.1702	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_7_m_pt_smq_wt_pp.sas using SAS 9.4

Table 12.4.4.1.6.s3.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Baseline Weight < 94.25 Kg vs 2.Baseline Weight ≥ 94.25 Kg

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.9704		0.3202		0.7025	
1.Baseline Weight < 94.25 Kg	N1=58	N1=30	N1=60	N1=24	N1=118	N1=54
n/N1 (%)	7/58 (12.1)	7/30 (23.3)	10/60 (16.7)	1/24 (4.2)	17/118 (14.4)	8/54 (14.8)
RR [95%-CI]; p-value	0.52 [0.20, 1.34], 0.1740		4.00 [0.54, 29.57], 0.1744		0.97 [0.45, 2.11], 0.9438	
OR [95%-CI]; p-value	0.45 [0.14, 1.44], 0.1709		4.60 [0.56, 38.10], 0.1250		0.97 [0.39, 2.40], 0.9438	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.06], 0.2019		0.13 [0.00, 0.25], 0.0475		-0.00 [-0.12, 0.11], 0.9441	
2.Baseline Weight≥ 94.25 Kg	N2=57	N2=32	N2=59	N2=36	N2=116	N2=68
n/N2 (%)	9/57 (15.8)	10/32 (31.3)	13/59 (22.0)	6/36 (16.7)	22/116 (19.0)	16/68 (23.5)
RR [95%-CI]; p-value	0.51 [0.23, 1.11], 0.0902		1.32 [0.55, 3.17], 0.5313		0.81 [0.46, 1.43], 0.4586	
OR [95%-CI]; p-value	0.41 [0.15, 1.16], 0.0876		1.41 [0.48, 4.12], 0.5258		0.76 [0.37, 1.57], 0.4604	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.03], 0.1041		0.05 [-0.11, 0.21], 0.5142		-0.05 [-0.17, 0.08], 0.4689	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s3_wt_pp/T12_4_4_1_6_m_pt_adr_wt_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.0464		0.7915		0.2215	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	48/65 (73.8)	30/41 (73.2)	53/83 (63.9)	25/39 (64.1)	101/148 (68.2)	55/80 (68.8)
RR [95%-CI]; p-value	1.01 [0.80, 1.28], 0.9389		1.00 [0.75, 1.32], 0.9788		0.99 [0.83, 1.19], 0.9372	
OR [95%-CI]; p-value	1.04 [0.43, 2.51], 0.9388		0.99 [0.45, 2.19], 0.9788		0.98 [0.54, 1.75], 0.9374	
RD [95%-CI]; p-value	0.01 [-0.17, 0.18], 0.9389		-0.00 [-0.19, 0.18], 0.9788		-0.01 [-0.13, 0.12], 0.9373	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	35/50 (70.0)	20/21 (95.2)	19/36 (52.8)	12/21 (57.1)	54/86 (62.8)	32/42 (76.2)
RR [95%-CI]; p-value	0.74 [0.60, 0.90], 0.0033		0.92 [0.57, 1.50], 0.7468		0.82 [0.65, 1.04], 0.1061	
OR [95%-CI]; p-value	0.12 [0.01, 0.95], 0.0202		0.84 [0.28, 2.48], 0.7496		0.53 [0.23, 1.21], 0.1295	
RD [95%-CI]; p-value	-0.25 [-0.41, -0.10], 0.0016		-0.04 [-0.31, 0.22], 0.7488		-0.13 [-0.30, 0.03], 0.1102	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.7280		0.2784		0.1762	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	7/41 (17.1)	6/83 (7.2)	2/39 (5.1)	13/148 (8.8)	9/80 (11.3)
RR [95%-CI]; p-value	0.63 [0.24, 1.67], 0.3528		1.41 [0.30, 6.67], 0.6651		0.78 [0.35, 1.75], 0.5469	
OR [95%-CI]; p-value	0.59 [0.19, 1.81], 0.3505		1.44 [0.28, 7.49], 0.6620		0.76 [0.31, 1.86], 0.5472	
RD [95%-CI]; p-value	-0.06 [-0.20, 0.07], 0.3694		0.02 [-0.07, 0.11], 0.6431		-0.02 [-0.11, 0.06], 0.5599	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	3/21 (14.3)	7/36 (19.4)	0/21 (0.0)	13/86 (15.1)	3/42 (7.1)
RR [95%-CI]; p-value	0.84 [0.23, 3.05], 0.7909		8.36 [0.50, 140.12], 0.1398		2.12 [0.64, 7.03], 0.2208	
OR [95%-CI]; p-value	0.82 [0.18, 3.63], 0.7916		10.14 [0.54, 188.64], 0.0622		2.32 [0.62, 8.62], 0.2003	
RD [95%-CI]; p-value	-0.02 [-0.20, 0.15], 0.7976		0.17 [0.03, 0.32], 0.0199		0.08 [-0.03, 0.19], 0.1502	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.4116		0.5538		0.7540	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	5/65 (7.7)	3/41 (7.3)	2/83 (2.4)	2/39 (5.1)	7/148 (4.7)	5/80 (6.3)
RR [95%-CI]; p-value	1.05 [0.27, 4.17], 0.9433		0.47 [0.07, 3.21], 0.4413		0.76 [0.25, 2.31], 0.6242	
OR [95%-CI]; p-value	1.06 [0.24, 4.67], 0.9432		0.46 [0.06, 3.37], 0.4317		0.74 [0.23, 2.43], 0.6237	
RD [95%-CI]; p-value	0.00 [-0.10, 0.11], 0.9429		-0.03 [-0.10, 0.05], 0.4872		-0.02 [-0.08, 0.05], 0.6368	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	1/21 (4.8)	1/36 (2.8)	3/21 (14.3)	8/86 (9.3)	4/42 (9.5)
RR [95%-CI]; p-value	2.94 [0.39, 22.44], 0.2983		0.19 [0.02, 1.75], 0.1443		0.98 [0.31, 3.06], 0.9678	
OR [95%-CI]; p-value	3.26 [0.37, 28.27], 0.2612		0.17 [0.02, 1.77], 0.1009		0.97 [0.28, 3.44], 0.9678	
RD [95%-CI]; p-value	0.09 [-0.04, 0.22], 0.1717		-0.12 [-0.27, 0.04], 0.1560		-0.00 [-0.11, 0.11], 0.9679	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.7803		0.5740		0.4971	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	9/65 (13.8)	6/41 (14.6)	6/83 (7.2)	4/39 (10.3)	15/148 (10.1)	10/80 (12.5)
RR [95%-CI]; p-value	0.95 [0.36, 2.46], 0.9097		0.70 [0.21, 2.36], 0.5699		0.81 [0.38, 1.72], 0.5849	
OR [95%-CI]; p-value	0.94 [0.31, 2.86], 0.9097		0.68 [0.18, 2.57], 0.5697		0.79 [0.34, 1.85], 0.5855	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.13], 0.9102		-0.03 [-0.14, 0.08], 0.5907		-0.02 [-0.11, 0.06], 0.5953	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	11/50 (22.0)	4/21 (19.0)	6/36 (16.7)	3/21 (14.3)	17/86 (19.8)	7/42 (16.7)
RR [95%-CI]; p-value	1.16 [0.41, 3.22], 0.7828		1.17 [0.33, 4.18], 0.8130		1.19 [0.53, 2.64], 0.6756	
OR [95%-CI]; p-value	1.20 [0.33, 4.30], 0.7809		1.20 [0.27, 5.40], 0.8120		1.23 [0.47, 3.25], 0.6730	
RD [95%-CI]; p-value	0.03 [-0.17, 0.23], 0.7761		0.02 [-0.17, 0.22], 0.8089		0.03 [-0.11, 0.17], 0.6657	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.2458		0.7710		0.4738	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	5/65 (7.7)	1/41 (2.4)	2/83 (2.4)	0/39 (0.0)	7/148 (4.7)	1/80 (1.3)
RR [95%-CI]; p-value	3.15 [0.38, 26.04], 0.2863		1.90 [0.09, 41.24], 0.6816		3.78 [0.47, 30.21], 0.2093	
OR [95%-CI]; p-value	3.33 [0.38, 29.61], 0.2543		1.93 [0.08, 43.72], 0.6756		3.92 [0.47, 32.46], 0.1729	
RD [95%-CI]; p-value	0.05 [-0.03, 0.13], 0.1990		0.01 [-0.04, 0.06], 0.6405		0.03 [-0.01, 0.08], 0.1042	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	3/50 (6.0)	2/21 (9.5)	3/36 (8.3)	0/21 (0.0)	6/86 (7.0)	2/42 (4.8)
RR [95%-CI]; p-value	0.63 [0.11, 3.50], 0.5975		3.58 [0.19, 68.18], 0.3958		1.47 [0.31, 6.95], 0.6307	
OR [95%-CI]; p-value	0.61 [0.09, 3.92], 0.5964		3.82 [0.18, 80.10], 0.3566		1.50 [0.29, 7.77], 0.6269	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6261		0.06 [-0.05, 0.17], 0.2866		0.02 [-0.06, 0.11], 0.6051	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8655		NA		0.9659	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	0/41 (0.0)	0/83 (0.0)	0/39 (0.0)	0/148 (0.0)	0/80 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	1/21 (4.8)	0/36 (0.0)	0/21 (0.0)	1/86 (1.2)	1/42 (2.4)
RR [95%-CI]; p-value	0.42 [0.03, 6.40], 0.5326		NA		0.49 [0.03, 7.62], 0.6091	
OR [95%-CI]; p-value	0.41 [0.02, 6.85], 0.5209		NA		0.48 [0.03, 7.91], 0.6018	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.07], 0.5845		NA		-0.01 [-0.06, 0.04], 0.6421	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.9067		NA		0.8196	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	1/41 (2.4)	0/83 (0.0)	0/39 (0.0)	0/148 (0.0)	1/80 (1.3)
RR [95%-CI]; p-value	0.31 [0.01, 9.12], 0.4996		NA		0.27 [0.01, 7.94], 0.4474	
OR [95%-CI]; p-value	0.31 [0.01, 9.38], 0.4752		NA		0.27 [0.01, 8.04], 0.4148	
RD [95%-CI]; p-value	-0.02 [-0.07, 0.03], 0.5253		NA		-0.01 [-0.04, 0.02], 0.4923	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	0/50 (0.0)	0/21 (0.0)	0/36 (0.0)	0/21 (0.0)	0/86 (0.0)	0/42 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.0329		0.6555		0.3217	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	40/65 (61.5)	26/41 (63.4)	44/83 (53.0)	21/39 (53.8)	84/148 (56.8)	47/80 (58.8)
RR [95%-CI]; p-value	0.97 [0.72, 1.31], 0.8453		0.98 [0.69, 1.40], 0.9312		0.97 [0.77, 1.22], 0.7699	
OR [95%-CI]; p-value	0.92 [0.41, 2.07], 0.8461		0.97 [0.45, 2.07], 0.9314		0.92 [0.53, 1.60], 0.7714	
RD [95%-CI]; p-value	-0.02 [-0.21, 0.17], 0.8457		-0.01 [-0.20, 0.18], 0.9313		-0.02 [-0.15, 0.11], 0.7710	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	28/50 (56.0)	19/21 (90.5)	16/36 (44.4)	8/21 (38.1)	44/86 (51.2)	27/42 (64.3)
RR [95%-CI]; p-value	0.62 [0.47, 0.82], 0.0009		1.17 [0.61, 2.25], 0.6452		0.80 [0.59, 1.08], 0.1432	
OR [95%-CI]; p-value	0.13 [0.03, 0.64], 0.0051		1.30 [0.43, 3.90], 0.6395		0.58 [0.27, 1.24], 0.1607	
RD [95%-CI]; p-value	-0.34 [-0.53, -0.16], 0.0003		0.06 [-0.20, 0.33], 0.6369		-0.13 [-0.31, 0.05], 0.1515	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.8524		0.3514		0.5201	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	23/65 (35.4)	17/41 (41.5)	24/83 (28.9)	8/39 (20.5)	47/148 (31.8)	25/80 (31.3)
RR [95%-CI]; p-value	0.85 [0.52, 1.39], 0.5261		1.41 [0.70, 2.85], 0.3391		1.02 [0.68, 1.52], 0.9375	
OR [95%-CI]; p-value	0.77 [0.35, 1.73], 0.5295		1.58 [0.63, 3.92], 0.3251		1.02 [0.57, 1.84], 0.9374	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5315		0.08 [-0.08, 0.24], 0.3031		0.01 [-0.12, 0.13], 0.9373	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	15/50 (30.0)	8/21 (38.1)	12/36 (33.3)	8/21 (38.1)	27/86 (31.4)	16/42 (38.1)
RR [95%-CI]; p-value	0.79 [0.39, 1.57], 0.4976		0.88 [0.43, 1.79], 0.7142		0.82 [0.50, 1.35], 0.4449	
OR [95%-CI]; p-value	0.70 [0.24, 2.03], 0.5059		0.81 [0.26, 2.49], 0.7163		0.74 [0.34, 1.61], 0.4511	
RD [95%-CI]; p-value	-0.08 [-0.32, 0.16], 0.5146		-0.05 [-0.31, 0.21], 0.7181		-0.07 [-0.24, 0.11], 0.4572	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.3.1.s4.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.4116		0.5538		0.7540	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	5/65 (7.7)	3/41 (7.3)	2/83 (2.4)	2/39 (5.1)	7/148 (4.7)	5/80 (6.3)
RR [95%-CI]; p-value	1.05 [0.27, 4.17], 0.9433		0.47 [0.07, 3.21], 0.4413		0.76 [0.25, 2.31], 0.6242	
OR [95%-CI]; p-value	1.06 [0.24, 4.67], 0.9432		0.46 [0.06, 3.37], 0.4317		0.74 [0.23, 2.43], 0.6237	
RD [95%-CI]; p-value	0.00 [-0.10, 0.11], 0.9429		-0.03 [-0.10, 0.05], 0.4872		-0.02 [-0.08, 0.05], 0.6368	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	1/21 (4.8)	1/36 (2.8)	3/21 (14.3)	8/86 (9.3)	4/42 (9.5)
RR [95%-CI]; p-value	2.94 [0.39, 22.44], 0.2983		0.19 [0.02, 1.75], 0.1443		0.98 [0.31, 3.06], 0.9678	
OR [95%-CI]; p-value	3.26 [0.37, 28.27], 0.2612		0.17 [0.02, 1.77], 0.1009		0.97 [0.28, 3.44], 0.9678	
RD [95%-CI]; p-value	0.09 [-0.04, 0.22], 0.1717		-0.12 [-0.27, 0.04], 0.1560		-0.00 [-0.11, 0.11], 0.9679	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_3_1_m_sf_ttl_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.8415		0.7485		0.7783	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	5/41 (12.2)	3/83 (3.6)	1/39 (2.6)	7/148 (4.7)	6/80 (7.5)
RR [95%-CI]; p-value	0.50 [0.14, 1.77], 0.2856		1.41 [0.15, 13.12], 0.7629		0.63 [0.22, 1.81], 0.3921	
OR [95%-CI]; p-value	0.47 [0.12, 1.87], 0.2772		1.43 [0.14, 14.15], 0.7613		0.61 [0.20, 1.89], 0.3893	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3072		0.01 [-0.05, 0.07], 0.7470		-0.03 [-0.09, 0.04], 0.4183	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	4/50 (8.0)	4/21 (19.0)	4/36 (11.1)	1/21 (4.8)	8/86 (9.3)	5/42 (11.9)
RR [95%-CI]; p-value	0.42 [0.12, 1.52], 0.1871		2.33 [0.28, 19.52], 0.4343		0.78 [0.27, 2.24], 0.6467	
OR [95%-CI]; p-value	0.37 [0.08, 1.65], 0.1791		2.50 [0.26, 23.99], 0.4137		0.76 [0.23, 2.48], 0.6472	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2393		0.06 [-0.07, 0.20], 0.3645		-0.03 [-0.14, 0.09], 0.6590	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4423		0.1555		0.1997	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	11/41 (26.8)	16/83 (19.3)	2/39 (5.1)	29/148 (19.6)	13/80 (16.3)
RR [95%-CI]; p-value	0.75 [0.37, 1.50], 0.4117		3.76 [0.91, 15.55], 0.0676		1.21 [0.67, 2.19], 0.5375	
OR [95%-CI]; p-value	0.68 [0.27, 1.71], 0.4132		4.42 [0.96, 20.28], 0.0399		1.26 [0.61, 2.58], 0.5341	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.10], 0.4225		0.14 [0.03, 0.25], 0.0113		0.03 [-0.07, 0.14], 0.5248	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	8/50 (16.0)	7/21 (33.3)	7/36 (19.4)	4/21 (19.0)	15/86 (17.4)	11/42 (26.2)
RR [95%-CI]; p-value	0.48 [0.20, 1.15], 0.1010		1.02 [0.34, 3.08], 0.9708		0.67 [0.34, 1.32], 0.2447	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1025		1.03 [0.26, 4.02], 0.9708		0.60 [0.25, 1.44], 0.2480	
RD [95%-CI]; p-value	-0.17 [-0.40, 0.05], 0.1324		0.00 [-0.21, 0.22], 0.9707		-0.09 [-0.24, 0.07], 0.2695	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8217		0.5654		0.5665	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	10/41 (24.4)	9/83 (10.8)	5/39 (12.8)	17/148 (11.5)	15/80 (18.8)
RR [95%-CI]; p-value	0.50 [0.22, 1.17], 0.1120		0.85 [0.30, 2.36], 0.7487		0.61 [0.32, 1.16], 0.1327	
OR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1066		0.83 [0.26, 2.65], 0.7493		0.56 [0.26, 1.20], 0.1318	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.03], 0.1236		-0.02 [-0.14, 0.10], 0.7555		-0.07 [-0.17, 0.03], 0.1536	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	5/21 (23.8)	5/36 (13.9)	2/21 (9.5)	12/86 (14.0)	7/42 (16.7)
RR [95%-CI]; p-value	0.59 [0.21, 1.64], 0.3114		1.46 [0.31, 6.86], 0.6331		0.84 [0.36, 1.97], 0.6841	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3141		1.53 [0.27, 8.70], 0.6281		0.81 [0.29, 2.24], 0.6852	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3506		0.04 [-0.13, 0.21], 0.6125		-0.03 [-0.16, 0.11], 0.6924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.6268		0.3277		0.3324	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	19/65 (29.2)	11/41 (26.8)	21/83 (25.3)	8/39 (20.5)	40/148 (27.0)	19/80 (23.8)
RR [95%-CI]; p-value	1.09 [0.58, 2.05], 0.7901		1.23 [0.60, 2.53], 0.5679		1.14 [0.71, 1.83], 0.5927	
OR [95%-CI]; p-value	1.13 [0.47, 2.70], 0.7892		1.31 [0.52, 3.30], 0.5623		1.19 [0.63, 2.23], 0.5897	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7879		0.05 [-0.11, 0.21], 0.5513		0.03 [-0.08, 0.15], 0.5848	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	12/50 (24.0)	6/21 (28.6)	7/36 (19.4)	6/21 (28.6)	19/86 (22.1)	12/42 (28.6)
RR [95%-CI]; p-value	0.84 [0.36, 1.94], 0.6831		0.68 [0.26, 1.76], 0.4264		0.77 [0.42, 1.44], 0.4173	
OR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6861		0.60 [0.17, 2.12], 0.4283		0.71 [0.31, 1.64], 0.4218	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.18], 0.6925		-0.09 [-0.32, 0.14], 0.4416		-0.06 [-0.23, 0.10], 0.4341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.9987		0.1455		0.2915	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	5/83 (6.0)	4/39 (10.3)	12/148 (8.1)	10/80 (12.5)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.59 [0.17, 2.07], 0.4073		0.65 [0.29, 1.43], 0.2852	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.56 [0.14, 2.22], 0.4043		0.62 [0.25, 1.50], 0.2838	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.04 [-0.15, 0.07], 0.4429		-0.04 [-0.13, 0.04], 0.3099	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	1/21 (4.8)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		3.50 [0.45, 27.12], 0.2304		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		4.00 [0.45, 35.79], 0.1865		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.12 [-0.03, 0.27], 0.1249		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8524		0.7540		0.6823	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	13/41 (31.7)	14/83 (16.9)	8/39 (20.5)	27/148 (18.2)	21/80 (26.3)
RR [95%-CI]; p-value	0.63 [0.33, 1.22], 0.1724		0.82 [0.38, 1.80], 0.6234		0.69 [0.42, 1.15], 0.1548	
OR [95%-CI]; p-value	0.54 [0.22, 1.32], 0.1725		0.79 [0.30, 2.07], 0.6253		0.63 [0.33, 1.20], 0.1570	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1834		-0.04 [-0.19, 0.11], 0.6342		-0.08 [-0.19, 0.03], 0.1714	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	10/50 (20.0)	6/21 (28.6)	7/36 (19.4)	4/21 (19.0)	17/86 (19.8)	10/42 (23.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.68], 0.4240		1.02 [0.34, 3.08], 0.9708		0.83 [0.42, 1.65], 0.5963	
OR [95%-CI]; p-value	0.63 [0.19, 2.02], 0.4302		1.03 [0.26, 4.02], 0.9708		0.79 [0.32, 1.91], 0.5987	
RD [95%-CI]; p-value	-0.09 [-0.31, 0.14], 0.4508		0.00 [-0.21, 0.22], 0.9707		-0.04 [-0.19, 0.11], 0.6066	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0292		0.6230		0.2304	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	14/65 (21.5)	10/41 (24.4)	11/83 (13.3)	8/39 (20.5)	25/148 (16.9)	18/80 (22.5)
RR [95%-CI]; p-value	0.88 [0.43, 1.80], 0.7318		0.65 [0.28, 1.48], 0.3008		0.75 [0.44, 1.29], 0.2993	
OR [95%-CI]; p-value	0.85 [0.34, 2.15], 0.7326		0.59 [0.22, 1.61], 0.3024		0.70 [0.36, 1.38], 0.3016	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.14], 0.7350		-0.07 [-0.22, 0.07], 0.3305		-0.06 [-0.17, 0.05], 0.3160	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	10/21 (47.6)	9/36 (25.0)	6/21 (28.6)	15/86 (17.4)	16/42 (38.1)
RR [95%-CI]; p-value	0.25 [0.11, 0.60], 0.0020		0.88 [0.36, 2.11], 0.7666		0.46 [0.25, 0.83], 0.0107	
OR [95%-CI]; p-value	0.15 [0.04, 0.50], 0.0010		0.83 [0.25, 2.80], 0.7677		0.34 [0.15, 0.79], 0.0104	
RD [95%-CI]; p-value	-0.36 [-0.59, -0.12], 0.0026		-0.04 [-0.28, 0.20], 0.7700		-0.21 [-0.37, -0.04], 0.0156	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.0801		0.6920		0.1021	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	9/41 (22.0)	7/83 (8.4)	4/39 (10.3)	11/148 (7.4)	13/80 (16.3)
RR [95%-CI]; p-value	0.28 [0.09, 0.85], 0.0249		0.82 [0.26, 2.64], 0.7427		0.46 [0.21, 0.97], 0.0424	
OR [95%-CI]; p-value	0.23 [0.07, 0.82], 0.0157		0.81 [0.22, 2.93], 0.7431		0.41 [0.18, 0.97], 0.0384	
RD [95%-CI]; p-value	-0.16 [-0.30, -0.02], 0.0265		-0.02 [-0.13, 0.09], 0.7507		-0.09 [-0.18, 0.00], 0.0581	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	2/21 (9.5)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	1.47 [0.33, 6.50], 0.6115		1.17 [0.33, 4.18], 0.8130		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	1.55 [0.29, 8.15], 0.6049		1.20 [0.27, 5.40], 0.8120		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	0.04 [-0.11, 0.20], 0.5791		0.02 [-0.17, 0.22], 0.8089		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.6713		0.9087		0.9169	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	5/41 (12.2)	3/83 (3.6)	1/39 (2.6)	6/148 (4.1)	6/80 (7.5)
RR [95%-CI]; p-value	0.38 [0.10, 1.50], 0.1667		1.41 [0.15, 13.12], 0.7629		0.54 [0.18, 1.62], 0.2723	
OR [95%-CI]; p-value	0.35 [0.08, 1.54], 0.1502		1.43 [0.14, 14.15], 0.7613		0.52 [0.16, 1.67], 0.2661	
RD [95%-CI]; p-value	-0.08 [-0.19, 0.04], 0.1863		0.01 [-0.05, 0.07], 0.7470		-0.03 [-0.10, 0.03], 0.3053	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	2/21 (9.5)	2/36 (5.6)	1/21 (4.8)	3/86 (3.5)	3/42 (7.1)
RR [95%-CI]; p-value	0.21 [0.02, 2.19], 0.1922		1.17 [0.11, 12.10], 0.8972		0.49 [0.10, 2.32], 0.3670	
OR [95%-CI]; p-value	0.19 [0.02, 2.27], 0.1504		1.18 [0.10, 13.81], 0.8970		0.47 [0.09, 2.43], 0.3584	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.06], 0.2618		0.01 [-0.11, 0.13], 0.8950		-0.04 [-0.12, 0.05], 0.4104	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8592		0.7351		0.8525	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	6/41 (14.6)	7/83 (8.4)	2/39 (5.1)	15/148 (10.1)	8/80 (10.0)
RR [95%-CI]; p-value	0.84 [0.31, 2.25], 0.7301		1.64 [0.36, 7.55], 0.5225		1.01 [0.45, 2.29], 0.9742	
OR [95%-CI]; p-value	0.82 [0.26, 2.56], 0.7304		1.70 [0.34, 8.61], 0.5148		1.02 [0.41, 2.51], 0.9742	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.11], 0.7345		0.03 [-0.06, 0.12], 0.4788		0.00 [-0.08, 0.08], 0.9742	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	7/42 (16.7)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		1.17 [0.33, 4.18], 0.8130		0.91 [0.39, 2.10], 0.8201	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		1.20 [0.27, 5.40], 0.8120		0.89 [0.33, 2.43], 0.8206	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.02 [-0.17, 0.22], 0.8089		-0.02 [-0.15, 0.12], 0.8229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5320		0.8298		0.6179	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	6/41 (14.6)	8/83 (9.6)	4/39 (10.3)	11/148 (7.4)	10/80 (12.5)
RR [95%-CI]; p-value	0.32 [0.08, 1.19], 0.0889		0.94 [0.30, 2.93], 0.9148		0.59 [0.26, 1.34], 0.2096	
OR [95%-CI]; p-value	0.28 [0.07, 1.20], 0.0715		0.93 [0.26, 3.31], 0.9149		0.56 [0.23, 1.39], 0.2066	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.02], 0.1007		-0.01 [-0.12, 0.11], 0.9157		-0.05 [-0.13, 0.03], 0.2364	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	3/50 (6.0)	2/21 (9.5)	4/36 (11.1)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	0.63 [0.11, 3.50], 0.5975		1.17 [0.23, 5.84], 0.8511		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	0.61 [0.09, 3.92], 0.5964		1.19 [0.20, 7.11], 0.8506		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6261		0.02 [-0.15, 0.18], 0.8479		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.1.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7082		0.7039		0.5252	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	4/83 (4.8)	5/39 (12.8)	11/148 (7.4)	11/80 (13.8)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.38 [0.11, 1.32], 0.1276		0.54 [0.25, 1.19], 0.1271	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.34 [0.09, 1.36], 0.1149		0.50 [0.21, 1.22], 0.1231	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.08 [-0.19, 0.03], 0.1712		-0.06 [-0.15, 0.02], 0.1522	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	2/21 (9.5)	2/36 (5.6)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	1.05 [0.22, 4.99], 0.9511		0.58 [0.09, 3.84], 0.5751		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	1.06 [0.19, 5.93], 0.9510		0.56 [0.07, 4.29], 0.5716		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9506		-0.04 [-0.19, 0.11], 0.5946		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_1_m_soc_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.3.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.7530		0.5400		0.6992	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	9/41 (22.0)	5/83 (6.0)	0/39 (0.0)	8/148 (5.4)	9/80 (11.3)
RR [95%-CI]; p-value	0.21 [0.06, 0.73], 0.0142		4.76 [0.27, 84.97], 0.2888		0.48 [0.19, 1.20], 0.1155	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0061		5.00 [0.27, 93.86], 0.2345		0.45 [0.17, 1.22], 0.1089	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.04], 0.0129		0.05 [-0.01, 0.11], 0.1321		-0.06 [-0.14, 0.02], 0.1432	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	3/21 (14.3)	1/36 (2.8)	0/21 (0.0)	2/86 (2.3)	3/42 (7.1)
RR [95%-CI]; p-value	0.14 [0.02, 1.27], 0.0805		1.19 [0.04, 34.13], 0.9173		0.33 [0.06, 1.87], 0.2090	
OR [95%-CI]; p-value	0.12 [0.01, 1.25], 0.0405		1.20 [0.04, 37.33], 0.9171		0.31 [0.05, 1.93], 0.1866	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.03], 0.1194		0.00 [-0.08, 0.09], 0.9153		-0.05 [-0.13, 0.04], 0.2619	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_3_m_pt_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.3.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.9305		0.2249		0.2238	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	2/65 (3.1)	5/41 (12.2)	7/83 (8.4)	1/39 (2.6)	9/148 (6.1)	6/80 (7.5)
RR [95%-CI]; p-value	0.25 [0.05, 1.24], 0.0901		3.29 [0.42, 25.82], 0.2574		0.81 [0.30, 2.20], 0.6800	
OR [95%-CI]; p-value	0.23 [0.04, 1.24], 0.0656		3.50 [0.42, 29.49], 0.2219		0.80 [0.27, 2.33], 0.6800	
RD [95%-CI]; p-value	-0.09 [-0.20, 0.02], 0.0999		0.06 [-0.02, 0.14], 0.1386		-0.01 [-0.08, 0.06], 0.6885	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	3/21 (14.3)	0/36 (0.0)	1/21 (4.8)	2/86 (2.3)	4/42 (9.5)
RR [95%-CI]; p-value	0.28 [0.05, 1.56], 0.1457		0.29 [0.01, 8.22], 0.4663		0.24 [0.05, 1.28], 0.0954	
OR [95%-CI]; p-value	0.25 [0.04, 1.62], 0.1221		0.28 [0.01, 8.65], 0.4372		0.23 [0.04, 1.29], 0.0704	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.06], 0.2054		-0.03 [-0.13, 0.06], 0.5001		-0.07 [-0.17, 0.02], 0.1347	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_3_m_pt_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.3.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.3645		0.8928		0.3907	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	3/41 (7.3)	3/83 (3.6)	4/39 (10.3)	6/148 (4.1)	7/80 (8.8)
RR [95%-CI]; p-value	0.63 [0.13, 2.98], 0.5606		0.35 [0.08, 1.50], 0.1580		0.46 [0.16, 1.33], 0.1533	
OR [95%-CI]; p-value	0.61 [0.12, 3.19], 0.5577		0.33 [0.07, 1.54], 0.1413		0.44 [0.14, 1.36], 0.1445	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.07], 0.5758		-0.07 [-0.17, 0.04], 0.2078		-0.05 [-0.12, 0.02], 0.1860	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	1/21 (4.8)	1/36 (2.8)	2/21 (9.5)	6/86 (7.0)	3/42 (7.1)
RR [95%-CI]; p-value	2.10 [0.26, 16.90], 0.4857		0.29 [0.03, 3.03], 0.3019		0.98 [0.26, 3.71], 0.9725	
OR [95%-CI]; p-value	2.22 [0.24, 20.27], 0.4689		0.27 [0.02, 3.19], 0.2712		0.98 [0.23, 4.11], 0.9725	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4052		-0.07 [-0.20, 0.07], 0.3329		-0.00 [-0.10, 0.09], 0.9726	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_3_m_pt_ae10pct_race_pp.sas using SAS 9.4

Table 12.4.8.1.1.s4.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.4631		0.6212		0.1947	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	1/41 (2.4)	1/83 (1.2)	2/39 (5.1)	1/148 (0.7)	3/80 (3.8)
RR [95%-CI]; p-value	0.31 [0.01, 9.12], 0.4996		0.23 [0.02, 2.51], 0.2310		0.18 [0.02, 1.70], 0.1349	
OR [95%-CI]; p-value	0.31 [0.01, 9.38], 0.4752		0.23 [0.02, 2.57], 0.1919		0.17 [0.02, 1.71], 0.0915	
RD [95%-CI]; p-value	-0.02 [-0.07, 0.03], 0.5253		-0.04 [-0.11, 0.03], 0.2928		-0.03 [-0.07, 0.01], 0.1677	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	0/21 (0.0)	1/36 (2.8)	1/21 (4.8)	3/86 (3.5)	1/42 (2.4)
RR [95%-CI]; p-value	1.72 [0.08, 36.59], 0.7281		0.58 [0.04, 8.85], 0.6976		1.47 [0.16, 13.66], 0.7374	
OR [95%-CI]; p-value	1.75 [0.08, 40.48], 0.7238		0.57 [0.03, 9.64], 0.6945		1.48 [0.15, 14.69], 0.7353	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6951		-0.02 [-0.13, 0.09], 0.7130		0.01 [-0.05, 0.07], 0.7186	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_8_1_1_m_soc_sae5pct_race_pp.sas using SAS 9.4

Table 12.4.8.1.2.s4.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_8_1_2_m_pt_sae5pct_race_pp.sas using SAS 9.4

Table 12.4.5.1.1.s4.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_5_1_1_m_soc_aeg35pct_race_pp.sas using SAS 9.4

Table 12.4.5.1.2.s4.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_5_1_2_m_pt_aeg35pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.4423		0.1555		0.1997	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	11/41 (26.8)	16/83 (19.3)	2/39 (5.1)	29/148 (19.6)	13/80 (16.3)
RR [95%-CI]; p-value	0.75 [0.37, 1.50], 0.4117		3.76 [0.91, 15.55], 0.0676		1.21 [0.67, 2.19], 0.5375	
OR [95%-CI]; p-value	0.68 [0.27, 1.71], 0.4132		4.42 [0.96, 20.28], 0.0399		1.26 [0.61, 2.58], 0.5341	
RD [95%-CI]; p-value	-0.07 [-0.24, 0.10], 0.4225		0.14 [0.03, 0.25], 0.0113		0.03 [-0.07, 0.14], 0.5248	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	8/50 (16.0)	7/21 (33.3)	7/36 (19.4)	4/21 (19.0)	15/86 (17.4)	11/42 (26.2)
RR [95%-CI]; p-value	0.48 [0.20, 1.15], 0.1010		1.02 [0.34, 3.08], 0.9708		0.67 [0.34, 1.32], 0.2447	
OR [95%-CI]; p-value	0.38 [0.12, 1.24], 0.1025		1.03 [0.26, 4.02], 0.9708		0.60 [0.25, 1.44], 0.2480	
RD [95%-CI]; p-value	-0.17 [-0.40, 0.05], 0.1324		0.00 [-0.21, 0.22], 0.9707		-0.09 [-0.24, 0.07], 0.2695	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.8217		0.5654		0.5665	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	10/41 (24.4)	9/83 (10.8)	5/39 (12.8)	17/148 (11.5)	15/80 (18.8)
RR [95%-CI]; p-value	0.50 [0.22, 1.17], 0.1120		0.85 [0.30, 2.36], 0.7487		0.61 [0.32, 1.16], 0.1327	
OR [95%-CI]; p-value	0.44 [0.16, 1.22], 0.1066		0.83 [0.26, 2.65], 0.7493		0.56 [0.26, 1.20], 0.1318	
RD [95%-CI]; p-value	-0.12 [-0.27, 0.03], 0.1236		-0.02 [-0.14, 0.10], 0.7555		-0.07 [-0.17, 0.03], 0.1536	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	5/21 (23.8)	5/36 (13.9)	2/21 (9.5)	12/86 (14.0)	7/42 (16.7)
RR [95%-CI]; p-value	0.59 [0.21, 1.64], 0.3114		1.46 [0.31, 6.86], 0.6331		0.84 [0.36, 1.97], 0.6841	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3141		1.53 [0.27, 8.70], 0.6281		0.81 [0.29, 2.24], 0.6852	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3506		0.04 [-0.13, 0.21], 0.6125		-0.03 [-0.16, 0.11], 0.6924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.6268		0.3277		0.3324	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	19/65 (29.2)	11/41 (26.8)	21/83 (25.3)	8/39 (20.5)	40/148 (27.0)	19/80 (23.8)
RR [95%-CI]; p-value	1.09 [0.58, 2.05], 0.7901		1.23 [0.60, 2.53], 0.5679		1.14 [0.71, 1.83], 0.5927	
OR [95%-CI]; p-value	1.13 [0.47, 2.70], 0.7892		1.31 [0.52, 3.30], 0.5623		1.19 [0.63, 2.23], 0.5897	
RD [95%-CI]; p-value	0.02 [-0.15, 0.20], 0.7879		0.05 [-0.11, 0.21], 0.5513		0.03 [-0.08, 0.15], 0.5848	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	12/50 (24.0)	6/21 (28.6)	7/36 (19.4)	6/21 (28.6)	19/86 (22.1)	12/42 (28.6)
RR [95%-CI]; p-value	0.84 [0.36, 1.94], 0.6831		0.68 [0.26, 1.76], 0.4264		0.77 [0.42, 1.44], 0.4173	
OR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6861		0.60 [0.17, 2.12], 0.4283		0.71 [0.31, 1.64], 0.4218	
RD [95%-CI]; p-value	-0.05 [-0.27, 0.18], 0.6925		-0.09 [-0.32, 0.14], 0.4416		-0.06 [-0.23, 0.10], 0.4341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.6921		0.5141		0.5743	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	9/65 (13.8)	4/41 (9.8)	5/83 (6.0)	2/39 (5.1)	14/148 (9.5)	6/80 (7.5)
RR [95%-CI]; p-value	1.42 [0.47, 4.31], 0.5368		1.17 [0.24, 5.79], 0.8432		1.26 [0.50, 3.15], 0.6198	
OR [95%-CI]; p-value	1.49 [0.43, 5.18], 0.5318		1.19 [0.22, 6.40], 0.8427		1.29 [0.48, 3.49], 0.6177	
RD [95%-CI]; p-value	0.04 [-0.08, 0.16], 0.5169		0.01 [-0.08, 0.10], 0.8384		0.02 [-0.05, 0.09], 0.6063	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	1/21 (4.8)	3/36 (8.3)	0/21 (0.0)	5/86 (5.8)	1/42 (2.4)
RR [95%-CI]; p-value	0.84 [0.08, 8.77], 0.8842		3.58 [0.19, 68.18], 0.3958		2.44 [0.29, 20.24], 0.4081	
OR [95%-CI]; p-value	0.83 [0.07, 9.72], 0.8842		3.82 [0.18, 80.10], 0.3566		2.53 [0.29, 22.38], 0.3883	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.10], 0.8880		0.06 [-0.05, 0.17], 0.2866		0.03 [-0.03, 0.10], 0.3197	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.9987		0.1455		0.2915	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	5/83 (6.0)	4/39 (10.3)	12/148 (8.1)	10/80 (12.5)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.59 [0.17, 2.07], 0.4073		0.65 [0.29, 1.43], 0.2852	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.56 [0.14, 2.22], 0.4043		0.62 [0.25, 1.50], 0.2838	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.04 [-0.15, 0.07], 0.4429		-0.04 [-0.13, 0.04], 0.3099	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	1/21 (4.8)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		3.50 [0.45, 27.12], 0.2304		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		4.00 [0.45, 35.79], 0.1865		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.12 [-0.03, 0.27], 0.1249		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.8524		0.7540		0.6823	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	13/65 (20.0)	13/41 (31.7)	14/83 (16.9)	8/39 (20.5)	27/148 (18.2)	21/80 (26.3)
RR [95%-CI]; p-value	0.63 [0.33, 1.22], 0.1724		0.82 [0.38, 1.80], 0.6234		0.69 [0.42, 1.15], 0.1548	
OR [95%-CI]; p-value	0.54 [0.22, 1.32], 0.1725		0.79 [0.30, 2.07], 0.6253		0.63 [0.33, 1.20], 0.1570	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.06], 0.1834		-0.04 [-0.19, 0.11], 0.6342		-0.08 [-0.19, 0.03], 0.1714	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	10/50 (20.0)	6/21 (28.6)	7/36 (19.4)	4/21 (19.0)	17/86 (19.8)	10/42 (23.8)
RR [95%-CI]; p-value	0.70 [0.29, 1.68], 0.4240		1.02 [0.34, 3.08], 0.9708		0.83 [0.42, 1.65], 0.5963	
OR [95%-CI]; p-value	0.63 [0.19, 2.02], 0.4302		1.03 [0.26, 4.02], 0.9708		0.79 [0.32, 1.91], 0.5987	
RD [95%-CI]; p-value	-0.09 [-0.31, 0.14], 0.4508		0.00 [-0.21, 0.22], 0.9707		-0.04 [-0.19, 0.11], 0.6066	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0292		0.6230		0.2304	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	14/65 (21.5)	10/41 (24.4)	11/83 (13.3)	8/39 (20.5)	25/148 (16.9)	18/80 (22.5)
RR [95%-CI]; p-value	0.88 [0.43, 1.80], 0.7318		0.65 [0.28, 1.48], 0.3008		0.75 [0.44, 1.29], 0.2993	
OR [95%-CI]; p-value	0.85 [0.34, 2.15], 0.7326		0.59 [0.22, 1.61], 0.3024		0.70 [0.36, 1.38], 0.3016	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.14], 0.7350		-0.07 [-0.22, 0.07], 0.3305		-0.06 [-0.17, 0.05], 0.3160	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	10/21 (47.6)	9/36 (25.0)	6/21 (28.6)	15/86 (17.4)	16/42 (38.1)
RR [95%-CI]; p-value	0.25 [0.11, 0.60], 0.0020		0.88 [0.36, 2.11], 0.7666		0.46 [0.25, 0.83], 0.0107	
OR [95%-CI]; p-value	0.15 [0.04, 0.50], 0.0010		0.83 [0.25, 2.80], 0.7677		0.34 [0.15, 0.79], 0.0104	
RD [95%-CI]; p-value	-0.36 [-0.59, -0.12], 0.0026		-0.04 [-0.28, 0.20], 0.7700		-0.21 [-0.37, -0.04], 0.0156	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.0801		0.6920		0.1021	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	9/41 (22.0)	7/83 (8.4)	4/39 (10.3)	11/148 (7.4)	13/80 (16.3)
RR [95%-CI]; p-value	0.28 [0.09, 0.85], 0.0249		0.82 [0.26, 2.64], 0.7427		0.46 [0.21, 0.97], 0.0424	
OR [95%-CI]; p-value	0.23 [0.07, 0.82], 0.0157		0.81 [0.22, 2.93], 0.7431		0.41 [0.18, 0.97], 0.0384	
RD [95%-CI]; p-value	-0.16 [-0.30, -0.02], 0.0265		-0.02 [-0.13, 0.09], 0.7507		-0.09 [-0.18, 0.00], 0.0581	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	2/21 (9.5)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	5/42 (11.9)
RR [95%-CI]; p-value	1.47 [0.33, 6.50], 0.6115		1.17 [0.33, 4.18], 0.8130		1.27 [0.48, 3.33], 0.6270	
OR [95%-CI]; p-value	1.55 [0.29, 8.15], 0.6049		1.20 [0.27, 5.40], 0.8120		1.32 [0.44, 3.98], 0.6236	
RD [95%-CI]; p-value	0.04 [-0.11, 0.20], 0.5791		0.02 [-0.17, 0.22], 0.8089		0.03 [-0.09, 0.16], 0.6111	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.8592		0.7351		0.8525	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	8/65 (12.3)	6/41 (14.6)	7/83 (8.4)	2/39 (5.1)	15/148 (10.1)	8/80 (10.0)
RR [95%-CI]; p-value	0.84 [0.31, 2.25], 0.7301		1.64 [0.36, 7.55], 0.5225		1.01 [0.45, 2.29], 0.9742	
OR [95%-CI]; p-value	0.82 [0.26, 2.56], 0.7304		1.70 [0.34, 8.61], 0.5148		1.02 [0.41, 2.51], 0.9742	
RD [95%-CI]; p-value	-0.02 [-0.16, 0.11], 0.7345		0.03 [-0.06, 0.12], 0.4788		0.00 [-0.08, 0.08], 0.9742	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	4/21 (19.0)	6/36 (16.7)	3/21 (14.3)	13/86 (15.1)	7/42 (16.7)
RR [95%-CI]; p-value	0.74 [0.24, 2.25], 0.5893		1.17 [0.33, 4.18], 0.8130		0.91 [0.39, 2.10], 0.8201	
OR [95%-CI]; p-value	0.69 [0.18, 2.67], 0.5916		1.20 [0.27, 5.40], 0.8120		0.89 [0.33, 2.43], 0.8206	
RD [95%-CI]; p-value	-0.05 [-0.24, 0.14], 0.6092		0.02 [-0.17, 0.22], 0.8089		-0.02 [-0.15, 0.12], 0.8229	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5320		0.8298		0.6179	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	6/41 (14.6)	8/83 (9.6)	4/39 (10.3)	11/148 (7.4)	10/80 (12.5)
RR [95%-CI]; p-value	0.32 [0.08, 1.19], 0.0889		0.94 [0.30, 2.93], 0.9148		0.59 [0.26, 1.34], 0.2096	
OR [95%-CI]; p-value	0.28 [0.07, 1.20], 0.0715		0.93 [0.26, 3.31], 0.9149		0.56 [0.23, 1.39], 0.2066	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.02], 0.1007		-0.01 [-0.12, 0.11], 0.9157		-0.05 [-0.13, 0.03], 0.2364	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	3/50 (6.0)	2/21 (9.5)	4/36 (11.1)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	0.63 [0.11, 3.50], 0.5975		1.17 [0.23, 5.84], 0.8511		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	0.61 [0.09, 3.92], 0.5964		1.19 [0.20, 7.11], 0.8506		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.11], 0.6261		0.02 [-0.15, 0.18], 0.8479		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.2.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.7082		0.7039		0.5252	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	7/65 (10.8)	6/41 (14.6)	4/83 (4.8)	5/39 (12.8)	11/148 (7.4)	11/80 (13.8)
RR [95%-CI]; p-value	0.74 [0.27, 2.04], 0.5549		0.38 [0.11, 1.32], 0.1276		0.54 [0.25, 1.19], 0.1271	
OR [95%-CI]; p-value	0.70 [0.22, 2.26], 0.5547		0.34 [0.09, 1.36], 0.1149		0.50 [0.21, 1.22], 0.1231	
RD [95%-CI]; p-value	-0.04 [-0.17, 0.09], 0.5656		-0.08 [-0.19, 0.03], 0.1712		-0.06 [-0.15, 0.02], 0.1522	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	2/21 (9.5)	2/36 (5.6)	2/21 (9.5)	7/86 (8.1)	4/42 (9.5)
RR [95%-CI]; p-value	1.05 [0.22, 4.99], 0.9511		0.58 [0.09, 3.84], 0.5751		0.85 [0.26, 2.76], 0.7928	
OR [95%-CI]; p-value	1.06 [0.19, 5.93], 0.9510		0.56 [0.07, 4.29], 0.5716		0.84 [0.23, 3.05], 0.7930	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9506		-0.04 [-0.19, 0.11], 0.5946		-0.01 [-0.12, 0.09], 0.7979	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_2_m_soc_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.4.s4.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.7530		0.5400		0.6992	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	9/41 (22.0)	5/83 (6.0)	0/39 (0.0)	8/148 (5.4)	9/80 (11.3)
RR [95%-CI]; p-value	0.21 [0.06, 0.73], 0.0142		4.76 [0.27, 84.97], 0.2888		0.48 [0.19, 1.20], 0.1155	
OR [95%-CI]; p-value	0.17 [0.04, 0.68], 0.0061		5.00 [0.27, 93.86], 0.2345		0.45 [0.17, 1.22], 0.1089	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.04], 0.0129		0.05 [-0.01, 0.11], 0.1321		-0.06 [-0.14, 0.02], 0.1432	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	3/21 (14.3)	1/36 (2.8)	0/21 (0.0)	2/86 (2.3)	3/42 (7.1)
RR [95%-CI]; p-value	0.14 [0.02, 1.27], 0.0805		1.19 [0.04, 34.13], 0.9173		0.33 [0.06, 1.87], 0.2090	
OR [95%-CI]; p-value	0.12 [0.01, 1.25], 0.0405		1.20 [0.04, 37.33], 0.9171		0.31 [0.05, 1.93], 0.1866	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.03], 0.1194		0.00 [-0.08, 0.09], 0.9153		-0.05 [-0.13, 0.04], 0.2619	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_4_m_pt_ae1pct_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.6952		0.0947		0.3205	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	6/65 (9.2)	1/41 (2.4)	2/83 (2.4)	4/39 (10.3)	8/148 (5.4)	5/80 (6.3)
RR [95%-CI]; p-value	3.78 [0.47, 30.31], 0.2099		0.23 [0.04, 1.23], 0.0861		0.86 [0.29, 2.56], 0.7929	
OR [95%-CI]; p-value	4.07 [0.47, 35.09], 0.1703		0.22 [0.04, 1.23], 0.0616		0.86 [0.27, 2.71], 0.7929	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1162		-0.08 [-0.18, 0.02], 0.1270		-0.01 [-0.07, 0.06], 0.7970	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	1/21 (4.8)	4/36 (11.1)	1/21 (4.8)	9/86 (10.5)	2/42 (4.8)
RR [95%-CI]; p-value	2.10 [0.26, 16.90], 0.4857		2.33 [0.28, 19.52], 0.4343		2.20 [0.50, 9.72], 0.2994	
OR [95%-CI]; p-value	2.22 [0.24, 20.27], 0.4689		2.50 [0.26, 23.99], 0.4137		2.34 [0.48, 11.34], 0.2797	
RD [95%-CI]; p-value	0.05 [-0.07, 0.18], 0.4052		0.06 [-0.07, 0.20], 0.3645		0.06 [-0.03, 0.15], 0.2208	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.9074		NA		0.8197	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	0/41 (0.0)	0/83 (0.0)	0/39 (0.0)	0/148 (0.0)	0/80 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	0/21 (0.0)	0/36 (0.0)	0/21 (0.0)	1/86 (1.2)	0/42 (0.0)
RR [95%-CI]; p-value	0.86 [0.03, 24.68], 0.9298		NA		0.99 [0.03, 28.88], 0.9946	
OR [95%-CI]; p-value	0.86 [0.03, 26.55], 0.9298		NA		0.99 [0.03, 30.05], 0.9946	
RD [95%-CI]; p-value	-0.00 [-0.08, 0.07], 0.9318		NA		-0.00 [-0.04, 0.04], 0.9946	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.5930		0.0947		0.3892	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	6/65 (9.2)	1/41 (2.4)	2/83 (2.4)	4/39 (10.3)	8/148 (5.4)	5/80 (6.3)
RR [95%-CI]; p-value	3.78 [0.47, 30.31], 0.2099		0.23 [0.04, 1.23], 0.0861		0.86 [0.29, 2.56], 0.7929	
OR [95%-CI]; p-value	4.07 [0.47, 35.09], 0.1703		0.22 [0.04, 1.23], 0.0616		0.86 [0.27, 2.71], 0.7929	
RD [95%-CI]; p-value	0.07 [-0.02, 0.15], 0.1162		-0.08 [-0.18, 0.02], 0.1270		-0.01 [-0.07, 0.06], 0.7970	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	4/50 (8.0)	1/21 (4.8)	4/36 (11.1)	1/21 (4.8)	8/86 (9.3)	2/42 (4.8)
RR [95%-CI]; p-value	1.68 [0.20, 14.15], 0.6333		2.33 [0.28, 19.52], 0.4343		1.95 [0.43, 8.80], 0.3832	
OR [95%-CI]; p-value	1.74 [0.18, 16.56], 0.6265		2.50 [0.26, 23.99], 0.4137		2.05 [0.42, 10.12], 0.3688	
RD [95%-CI]; p-value	0.03 [-0.09, 0.15], 0.5910		0.06 [-0.07, 0.20], 0.3645		0.05 [-0.04, 0.13], 0.3172	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.9606		0.7242		0.7508	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	3/65 (4.6)	1/41 (2.4)	0/83 (0.0)	0/39 (0.0)	3/148 (2.0)	1/80 (1.3)
RR [95%-CI]; p-value	1.89 [0.20, 17.58], 0.5750		NA		1.62 [0.17, 15.34], 0.6732	
OR [95%-CI]; p-value	1.94 [0.19, 19.26], 0.5669		NA		1.63 [0.17, 15.98], 0.6697	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.5394		NA		0.01 [-0.03, 0.04], 0.6473	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	0/21 (0.0)	1/36 (2.8)	0/21 (0.0)	3/86 (3.5)	0/42 (0.0)
RR [95%-CI]; p-value	1.72 [0.08, 36.59], 0.7281		1.19 [0.04, 34.13], 0.9173		2.97 [0.15, 57.87], 0.4734	
OR [95%-CI]; p-value	1.75 [0.08, 40.48], 0.7238		1.20 [0.04, 37.33], 0.9171		3.04 [0.15, 62.02], 0.4488	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6951		0.00 [-0.08, 0.09], 0.9153		0.02 [-0.03, 0.07], 0.3700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.7990		0.4348		0.4533	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	5/41 (12.2)	4/83 (4.8)	3/39 (7.7)	8/148 (5.4)	8/80 (10.0)
RR [95%-CI]; p-value	0.50 [0.14, 1.77], 0.2856		0.63 [0.15, 2.66], 0.5267		0.54 [0.21, 1.39], 0.2003	
OR [95%-CI]; p-value	0.47 [0.12, 1.87], 0.2772		0.61 [0.13, 2.86], 0.5246		0.51 [0.19, 1.43], 0.1949	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3072		-0.03 [-0.12, 0.07], 0.5554		-0.05 [-0.12, 0.03], 0.2309	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	6/50 (12.0)	4/21 (19.0)	5/36 (13.9)	2/21 (9.5)	11/86 (12.8)	6/42 (14.3)
RR [95%-CI]; p-value	0.63 [0.20, 2.01], 0.4342		1.46 [0.31, 6.86], 0.6331		0.90 [0.36, 2.26], 0.8146	
OR [95%-CI]; p-value	0.58 [0.15, 2.31], 0.4359		1.53 [0.27, 8.70], 0.6281		0.88 [0.30, 2.57], 0.8150	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.12], 0.4686		0.04 [-0.13, 0.21], 0.6125		-0.01 [-0.14, 0.11], 0.8178	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.9074		0.8247		0.9593	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	0/65 (0.0)	0/41 (0.0)	1/83 (1.2)	0/39 (0.0)	1/148 (0.7)	0/80 (0.0)
RR [95%-CI]; p-value	NA		0.95 [0.03, 27.78], 0.9771		1.09 [0.04, 32.08], 0.9611	
OR [95%-CI]; p-value	NA		0.95 [0.03, 28.96], 0.9771		1.09 [0.04, 32.80], 0.9611	
RD [95%-CI]; p-value	NA		-0.00 [-0.04, 0.04], 0.9773		0.00 [-0.02, 0.02], 0.9606	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	1/50 (2.0)	0/21 (0.0)	1/36 (2.8)	1/21 (4.8)	2/86 (2.3)	1/42 (2.4)
RR [95%-CI]; p-value	0.86 [0.03, 24.68], 0.9298		0.58 [0.04, 8.85], 0.6976		0.98 [0.09, 10.47], 0.9845	
OR [95%-CI]; p-value	0.86 [0.03, 26.55], 0.9298		0.57 [0.03, 9.64], 0.6945		0.98 [0.09, 11.08], 0.9845	
RD [95%-CI]; p-value	-0.00 [-0.08, 0.07], 0.9318		-0.02 [-0.13, 0.09], 0.7130		-0.00 [-0.06, 0.06], 0.9845	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.9645		0.5735		0.6585	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	4/65 (6.2)	5/41 (12.2)	4/83 (4.8)	3/39 (7.7)	8/148 (5.4)	8/80 (10.0)
RR [95%-CI]; p-value	0.50 [0.14, 1.77], 0.2856		0.63 [0.15, 2.66], 0.5267		0.54 [0.21, 1.39], 0.2003	
OR [95%-CI]; p-value	0.47 [0.12, 1.87], 0.2772		0.61 [0.13, 2.86], 0.5246		0.51 [0.19, 1.43], 0.1949	
RD [95%-CI]; p-value	-0.06 [-0.18, 0.06], 0.3072		-0.03 [-0.12, 0.07], 0.5554		-0.05 [-0.12, 0.03], 0.2309	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	5/50 (10.0)	4/21 (19.0)	4/36 (11.1)	2/21 (9.5)	9/86 (10.5)	6/42 (14.3)
RR [95%-CI]; p-value	0.53 [0.16, 1.76], 0.2974		1.17 [0.23, 5.84], 0.8511		0.73 [0.28, 1.92], 0.5273	
OR [95%-CI]; p-value	0.47 [0.11, 1.97], 0.2957		1.19 [0.20, 7.11], 0.8506		0.70 [0.23, 2.12], 0.5280	
RD [95%-CI]; p-value	-0.09 [-0.28, 0.10], 0.3440		0.02 [-0.15, 0.18], 0.8479		-0.04 [-0.16, 0.09], 0.5460	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.7.s4.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8582		0.9226		0.7847	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	2/65 (3.1)	0/41 (0.0)	1/83 (1.2)	0/39 (0.0)	3/148 (2.0)	0/80 (0.0)
RR [95%-CI]; p-value	2.55 [0.12, 55.26], 0.5500		0.95 [0.03, 27.78], 0.9771		3.26 [0.17, 64.35], 0.4368	
OR [95%-CI]; p-value	2.60 [0.11, 59.18], 0.5337		0.95 [0.03, 28.96], 0.9771		3.31 [0.16, 66.91], 0.4085	
RD [95%-CI]; p-value	0.02 [-0.03, 0.07], 0.4930		-0.00 [-0.04, 0.04], 0.9773		0.01 [-0.01, 0.04], 0.3330	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	2/50 (4.0)	0/21 (0.0)	2/36 (5.6)	1/21 (4.8)	4/86 (4.7)	1/42 (2.4)
RR [95%-CI]; p-value	1.72 [0.08, 36.59], 0.7281		1.17 [0.11, 12.10], 0.8972		1.95 [0.23, 16.94], 0.5435	
OR [95%-CI]; p-value	1.75 [0.08, 40.48], 0.7238		1.18 [0.10, 13.81], 0.8970		2.00 [0.22, 18.47], 0.5336	
RD [95%-CI]; p-value	0.02 [-0.07, 0.10], 0.6951		0.01 [-0.11, 0.13], 0.8950		0.02 [-0.04, 0.09], 0.4875	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_7_m_pt_smq_race_pp.sas using SAS 9.4

Table 12.4.4.1.6.s4.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.White vs 2.non-White

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.9350		0.3618		0.4157	
1.White	N1=65	N1=41	N1=83	N1=39	N1=148	N1=80
n/N1 (%)	9/65 (13.8)	11/41 (26.8)	18/83 (21.7)	4/39 (10.3)	27/148 (18.2)	15/80 (18.8)
RR [95%-CI]; p-value	0.52 [0.23, 1.14], 0.1005		2.11 [0.77, 5.83], 0.1480		0.97 [0.55, 1.72], 0.9249	
OR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.0961		2.42 [0.76, 7.72], 0.1257		0.97 [0.48, 1.95], 0.9249	
RD [95%-CI]; p-value	-0.13 [-0.29, 0.03], 0.1106		0.11 [-0.02, 0.24], 0.0851		-0.01 [-0.11, 0.10], 0.9252	
2.non-White	N2=50	N2=21	N2=36	N2=21	N2=86	N2=42
n/N2 (%)	7/50 (14.0)	6/21 (28.6)	5/36 (13.9)	3/21 (14.3)	12/86 (14.0)	9/42 (21.4)
RR [95%-CI]; p-value	0.49 [0.19, 1.28], 0.1470		0.97 [0.26, 3.66], 0.9668		0.65 [0.30, 1.42], 0.2820	
OR [95%-CI]; p-value	0.41 [0.12, 1.40], 0.1474		0.97 [0.21, 4.54], 0.9668		0.59 [0.23, 1.55], 0.2836	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.07], 0.1858		-0.00 [-0.19, 0.18], 0.9669		-0.07 [-0.22, 0.07], 0.3093	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s4_race_pp/T12_4_4_1_6_m_pt_adr_race_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.8862		0.9318		0.8482	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	42/58 (72.4)	27/33 (81.8)	38/65 (58.5)	17/29 (58.6)	80/123 (65.0)	44/62 (71.0)
RR [95%-CI]; p-value	0.89 [0.71, 1.11], 0.2897		1.00 [0.69, 1.44], 0.9885		0.92 [0.75, 1.13], 0.4050	
OR [95%-CI]; p-value	0.58 [0.20, 1.68], 0.3138		0.99 [0.41, 2.42], 0.9885		0.76 [0.39, 1.48], 0.4182	
RD [95%-CI]; p-value	-0.09 [-0.27, 0.08], 0.2916		-0.00 [-0.22, 0.21], 0.9885		-0.06 [-0.20, 0.08], 0.4098	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	41/57 (71.9)	23/29 (79.3)	34/54 (63.0)	20/31 (64.5)	75/111 (67.6)	43/60 (71.7)
RR [95%-CI]; p-value	0.91 [0.71, 1.16], 0.4377		0.98 [0.70, 1.36], 0.8855		0.94 [0.77, 1.16], 0.5729	
OR [95%-CI]; p-value	0.67 [0.23, 1.95], 0.4583		0.94 [0.37, 2.35], 0.8861		0.82 [0.41, 1.64], 0.5802	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.11], 0.4416		-0.02 [-0.23, 0.20], 0.8858		-0.04 [-0.18, 0.10], 0.5755	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.4828		0.6798		0.4022	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	7/33 (21.2)	5/65 (7.7)	0/29 (0.0)	12/123 (9.8)	7/62 (11.3)
RR [95%-CI]; p-value	0.57 [0.22, 1.48], 0.2479		4.54 [0.26, 80.39], 0.3024		0.86 [0.36, 2.08], 0.7452	
OR [95%-CI]; p-value	0.51 [0.16, 1.61], 0.2452		4.83 [0.26, 91.49], 0.2485		0.85 [0.32, 2.28], 0.7456	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2708		0.06 [-0.02, 0.14], 0.1407		-0.02 [-0.11, 0.08], 0.7507	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	3/29 (10.3)	8/54 (14.8)	2/31 (6.5)	14/111 (12.6)	5/60 (8.3)
RR [95%-CI]; p-value	1.02 [0.27, 3.78], 0.9793		2.30 [0.52, 10.14], 0.2726		1.51 [0.57, 4.00], 0.4032	
OR [95%-CI]; p-value	1.02 [0.24, 4.41], 0.9793		2.52 [0.50, 12.71], 0.2493		1.59 [0.54, 4.64], 0.3954	
RD [95%-CI]; p-value	0.00 [-0.13, 0.14], 0.9792		0.08 [-0.04, 0.21], 0.2013		0.04 [-0.05, 0.14], 0.3687	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.6045		0.7179		0.8453	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	3/33 (9.1)	1/65 (1.5)	2/29 (6.9)	8/123 (6.5)	5/62 (8.1)
RR [95%-CI]; p-value	1.33 [0.37, 4.79], 0.6652		0.22 [0.02, 2.36], 0.2128		0.81 [0.28, 2.36], 0.6950	
OR [95%-CI]; p-value	1.37 [0.33, 5.71], 0.6623		0.21 [0.02, 2.43], 0.1722		0.79 [0.25, 2.53], 0.6951	
RD [95%-CI]; p-value	0.03 [-0.10, 0.16], 0.6510		-0.05 [-0.15, 0.04], 0.2788		-0.02 [-0.10, 0.06], 0.7043	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	1/29 (3.4)	2/54 (3.7)	3/31 (9.7)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	2.54 [0.31, 20.77], 0.3835		0.38 [0.07, 2.17], 0.2776		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	2.69 [0.30, 24.19], 0.3596		0.36 [0.06, 2.28], 0.2599		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.2920		-0.06 [-0.18, 0.06], 0.3112		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.8774		0.3026		0.4469	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	12/58 (20.7)	6/33 (18.2)	7/65 (10.8)	2/29 (6.9)	19/123 (15.4)	8/62 (12.9)
RR [95%-CI]; p-value	1.14 [0.47, 2.75], 0.7740		1.56 [0.35, 7.06], 0.5628		1.20 [0.56, 2.58], 0.6459	
OR [95%-CI]; p-value	1.17 [0.40, 3.49], 0.7728		1.63 [0.32, 8.37], 0.5556		1.23 [0.51, 3.00], 0.6436	
RD [95%-CI]; p-value	0.03 [-0.14, 0.19], 0.7697		0.04 [-0.08, 0.16], 0.5239		0.03 [-0.08, 0.13], 0.6352	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	4/29 (13.8)	5/54 (9.3)	5/31 (16.1)	13/111 (11.7)	9/60 (15.0)
RR [95%-CI]; p-value	1.02 [0.33, 3.10], 0.9756		0.57 [0.18, 1.83], 0.3476		0.78 [0.35, 1.72], 0.5391	
OR [95%-CI]; p-value	1.02 [0.28, 3.72], 0.9756		0.53 [0.14, 2.00], 0.3440		0.75 [0.30, 1.88], 0.5399	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9755		-0.07 [-0.22, 0.08], 0.3719		-0.03 [-0.14, 0.08], 0.5520	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.6733		0.9434		0.6462	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	4/58 (6.9)	2/33 (6.1)	3/65 (4.6)	0/29 (0.0)	7/123 (5.7)	2/62 (3.2)
RR [95%-CI]; p-value	1.14 [0.22, 5.88], 0.8775		2.72 [0.14, 52.66], 0.5074		1.76 [0.38, 8.24], 0.4704	
OR [95%-CI]; p-value	1.15 [0.20, 6.63], 0.8772		2.81 [0.14, 57.86], 0.4861		1.81 [0.36, 8.99], 0.4619	
RD [95%-CI]; p-value	0.01 [-0.10, 0.11], 0.8752		0.03 [-0.04, 0.10], 0.4073		0.02 [-0.04, 0.08], 0.4213	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	1/29 (3.4)	2/54 (3.7)	0/31 (0.0)	6/111 (5.4)	1/60 (1.7)
RR [95%-CI]; p-value	2.04 [0.24, 17.39], 0.5162		2.33 [0.11, 50.15], 0.5883		3.24 [0.40, 26.32], 0.2707	
OR [95%-CI]; p-value	2.11 [0.23, 19.82], 0.5037		2.38 [0.10, 54.59], 0.5753		3.37 [0.40, 28.68], 0.2390	
RD [95%-CI]; p-value	0.04 [-0.06, 0.13], 0.4560		0.02 [-0.05, 0.09], 0.5337		0.04 [-0.02, 0.09], 0.1675	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9612		NA		0.9785	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	0/33 (0.0)	0/65 (0.0)	0/29 (0.0)	0/123 (0.0)	0/62 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	1/29 (3.4)	0/54 (0.0)	0/31 (0.0)	1/111 (0.9)	1/60 (1.7)
RR [95%-CI]; p-value	0.51 [0.03, 7.84], 0.6283		NA		0.54 [0.03, 8.49], 0.6615	
OR [95%-CI]; p-value	0.50 [0.03, 8.29], 0.6222		NA		0.54 [0.03, 8.73], 0.6567	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.06], 0.6565		NA		-0.01 [-0.04, 0.03], 0.6838	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.8199		NA		0.7700	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	1/33 (3.0)	0/65 (0.0)	0/29 (0.0)	0/123 (0.0)	1/62 (1.6)
RR [95%-CI]; p-value	0.28 [0.01, 8.18], 0.4614		NA		0.25 [0.01, 7.38], 0.4230	
OR [95%-CI]; p-value	0.28 [0.01, 8.45], 0.4313		NA		0.25 [0.01, 7.49], 0.3861	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.04], 0.4989		NA		-0.01 [-0.05, 0.02], 0.4770	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	0/57 (0.0)	0/29 (0.0)	0/54 (0.0)	0/31 (0.0)	0/111 (0.0)	0/60 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.7085		0.4265		0.3327	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	36/58 (62.1)	26/33 (78.8)	33/65 (50.8)	16/29 (55.2)	69/123 (56.1)	42/62 (67.7)
RR [95%-CI]; p-value	0.79 [0.60, 1.03], 0.0811		0.92 [0.61, 1.38], 0.6881		0.83 [0.66, 1.04], 0.1115	
OR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.0999		0.84 [0.35, 2.02], 0.6931		0.61 [0.32, 1.15], 0.1270	
RD [95%-CI]; p-value	-0.17 [-0.35, 0.02], 0.0801		-0.04 [-0.26, 0.17], 0.6922		-0.12 [-0.26, 0.03], 0.1173	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	32/57 (56.1)	19/29 (65.5)	27/54 (50.0)	13/31 (41.9)	59/111 (53.2)	32/60 (53.3)
RR [95%-CI]; p-value	0.86 [0.60, 1.22], 0.3868		1.19 [0.73, 1.95], 0.4841		1.00 [0.74, 1.34], 0.9820	
OR [95%-CI]; p-value	0.67 [0.27, 1.70], 0.4027		1.38 [0.57, 3.37], 0.4734		0.99 [0.53, 1.86], 0.9820	
RD [95%-CI]; p-value	-0.09 [-0.31, 0.12], 0.3942		0.08 [-0.14, 0.30], 0.4704		-0.00 [-0.16, 0.15], 0.9820	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.5521		0.0281		0.0645	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	21/58 (36.2)	13/33 (39.4)	22/65 (33.8)	4/29 (13.8)	43/123 (35.0)	17/62 (27.4)
RR [95%-CI]; p-value	0.92 [0.53, 1.58], 0.7611		2.45 [0.93, 6.48], 0.0701		1.27 [0.80, 2.04], 0.3123	
OR [95%-CI]; p-value	0.87 [0.36, 2.11], 0.7625		3.20 [0.99, 10.34], 0.0447		1.42 [0.73, 2.78], 0.3011	
RD [95%-CI]; p-value	-0.03 [-0.24, 0.18], 0.7635		0.20 [0.03, 0.37], 0.0210		0.08 [-0.06, 0.21], 0.2891	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	17/57 (29.8)	12/29 (41.4)	14/54 (25.9)	12/31 (38.7)	31/111 (27.9)	24/60 (40.0)
RR [95%-CI]; p-value	0.72 [0.40, 1.30], 0.2754		0.67 [0.36, 1.26], 0.2138		0.70 [0.45, 1.07], 0.1019	
OR [95%-CI]; p-value	0.60 [0.24, 1.53], 0.2839		0.55 [0.22, 1.43], 0.2182		0.58 [0.30, 1.13], 0.1068	
RD [95%-CI]; p-value	-0.12 [-0.33, 0.10], 0.2922		-0.13 [-0.34, 0.08], 0.2273		-0.12 [-0.27, 0.03], 0.1133	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s5.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.6045		0.7179		0.8453	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	3/33 (9.1)	1/65 (1.5)	2/29 (6.9)	8/123 (6.5)	5/62 (8.1)
RR [95%-CI]; p-value	1.33 [0.37, 4.79], 0.6652		0.22 [0.02, 2.36], 0.2128		0.81 [0.28, 2.36], 0.6950	
OR [95%-CI]; p-value	1.37 [0.33, 5.71], 0.6623		0.21 [0.02, 2.43], 0.1722		0.79 [0.25, 2.53], 0.6951	
RD [95%-CI]; p-value	0.03 [-0.10, 0.16], 0.6510		-0.05 [-0.15, 0.04], 0.2788		-0.02 [-0.10, 0.06], 0.7043	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	1/29 (3.4)	2/54 (3.7)	3/31 (9.7)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	2.54 [0.31, 20.77], 0.3835		0.38 [0.07, 2.17], 0.2776		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	2.69 [0.30, 24.19], 0.3596		0.36 [0.06, 2.28], 0.2599		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.2920		-0.06 [-0.18, 0.06], 0.3112		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_3_1_m_sf_ttl_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.9039		0.4288		0.5257	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	4/58 (6.9)	5/33 (15.2)	4/65 (6.2)	2/29 (6.9)	8/123 (6.5)	7/62 (11.3)
RR [95%-CI]; p-value	0.46 [0.13, 1.58], 0.2147		0.89 [0.17, 4.60], 0.8917		0.58 [0.22, 1.52], 0.2638	
OR [95%-CI]; p-value	0.41 [0.10, 1.67], 0.2047		0.89 [0.15, 5.13], 0.8918		0.55 [0.19, 1.58], 0.2603	
RD [95%-CI]; p-value	-0.08 [-0.22, 0.06], 0.2432		-0.01 [-0.12, 0.10], 0.8939		-0.05 [-0.14, 0.04], 0.2974	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	4/29 (13.8)	3/54 (5.6)	0/31 (0.0)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3127		3.50 [0.18, 67.64], 0.4070		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3065		3.65 [0.18, 75.26], 0.3717		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3495		0.04 [-0.04, 0.11], 0.3003		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.2944		0.2435		0.1577	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	13/58 (22.4)	9/33 (27.3)	15/65 (23.1)	2/29 (6.9)	28/123 (22.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.82 [0.39, 1.71], 0.6006		3.35 [0.82, 13.69], 0.0929		1.28 [0.69, 2.40], 0.4359	
OR [95%-CI]; p-value	0.77 [0.29, 2.06], 0.6027		4.05 [0.86, 19.04], 0.0598		1.37 [0.63, 2.97], 0.4292	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.14], 0.6087		0.16 [0.02, 0.30], 0.0214		0.05 [-0.07, 0.17], 0.4142	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	8/54 (14.8)	4/31 (12.9)	16/111 (14.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		1.15 [0.38, 3.50], 0.8083		0.67 [0.34, 1.29], 0.2269	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		1.17 [0.32, 4.27], 0.8075		0.61 [0.27, 1.37], 0.2278	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		0.02 [-0.13, 0.17], 0.8045		-0.07 [-0.20, 0.05], 0.2479	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.5656		0.4841		0.4231	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	9/58 (15.5)	8/33 (24.2)	9/65 (13.8)	3/29 (10.3)	18/123 (14.6)	11/62 (17.7)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3042		1.34 [0.39, 4.58], 0.6426		0.82 [0.42, 1.64], 0.5817	
OR [95%-CI]; p-value	0.57 [0.20, 1.67], 0.3046		1.39 [0.35, 5.58], 0.6385		0.79 [0.35, 1.81], 0.5831	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3240		0.04 [-0.10, 0.17], 0.6216		-0.03 [-0.14, 0.08], 0.5924	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	7/29 (24.1)	5/54 (9.3)	4/31 (12.9)	11/111 (9.9)	11/60 (18.3)
RR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.1020		0.72 [0.21, 2.48], 0.5994		0.54 [0.25, 1.17], 0.1195	
OR [95%-CI]; p-value	0.37 [0.11, 1.23], 0.0957		0.69 [0.17, 2.78], 0.5992		0.49 [0.20, 1.21], 0.1164	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1273		-0.04 [-0.18, 0.10], 0.6127		-0.08 [-0.20, 0.03], 0.1425	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.9095		0.2897		0.4332	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	16/58 (27.6)	9/33 (27.3)	18/65 (27.7)	6/29 (20.7)	34/123 (27.6)	15/62 (24.2)
RR [95%-CI]; p-value	1.01 [0.50, 2.03], 0.9743		1.34 [0.59, 3.02], 0.4826		1.14 [0.68, 1.93], 0.6190	
OR [95%-CI]; p-value	1.02 [0.39, 2.65], 0.9743		1.47 [0.51, 4.20], 0.4720		1.20 [0.59, 2.42], 0.6158	
RD [95%-CI]; p-value	0.00 [-0.19, 0.19], 0.9743		0.07 [-0.11, 0.25], 0.4538		0.03 [-0.10, 0.17], 0.6105	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	15/57 (26.3)	8/29 (27.6)	10/54 (18.5)	8/31 (25.8)	25/111 (22.5)	16/60 (26.7)
RR [95%-CI]; p-value	0.95 [0.46, 1.98], 0.8996		0.72 [0.32, 1.63], 0.4266		0.84 [0.49, 1.45], 0.5423	
OR [95%-CI]; p-value	0.94 [0.34, 2.56], 0.8999		0.65 [0.23, 1.88], 0.4286		0.80 [0.39, 1.65], 0.5447	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9003		-0.07 [-0.26, 0.11], 0.4416		-0.04 [-0.18, 0.09], 0.5510	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.8839		0.2850		0.5047	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	5/33 (15.2)	6/65 (9.2)	1/29 (3.4)	13/123 (10.6)	6/62 (9.7)
RR [95%-CI]; p-value	0.80 [0.27, 2.31], 0.6755		2.68 [0.34, 21.24], 0.3515		1.09 [0.44, 2.73], 0.8507	
OR [95%-CI]; p-value	0.77 [0.22, 2.65], 0.6761		2.85 [0.33, 24.80], 0.3240		1.10 [0.40, 3.06], 0.8504	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.12], 0.6837		0.06 [-0.04, 0.15], 0.2415		0.01 [-0.08, 0.10], 0.8485	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	5/29 (17.2)	5/54 (9.3)	4/31 (12.9)	12/111 (10.8)	9/60 (15.0)
RR [95%-CI]; p-value	0.71 [0.25, 2.05], 0.5293		0.72 [0.21, 2.48], 0.5994		0.72 [0.32, 1.61], 0.4253	
OR [95%-CI]; p-value	0.67 [0.19, 2.34], 0.5302		0.69 [0.17, 2.78], 0.5992		0.69 [0.27, 1.74], 0.4257	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5478		-0.04 [-0.18, 0.10], 0.6127		-0.04 [-0.15, 0.07], 0.4439	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5859		0.0578		0.0694	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	11/58 (19.0)	11/33 (33.3)	7/65 (10.8)	7/29 (24.1)	18/123 (14.6)	18/62 (29.0)
RR [95%-CI]; p-value	0.57 [0.28, 1.17], 0.1238		0.45 [0.17, 1.16], 0.0965		0.50 [0.28, 0.90], 0.0201	
OR [95%-CI]; p-value	0.47 [0.18, 1.24], 0.1238		0.38 [0.12, 1.21], 0.0927		0.42 [0.20, 0.88], 0.0195	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1380		-0.13 [-0.31, 0.04], 0.1299		-0.14 [-0.27, -0.01], 0.0288	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	12/57 (21.1)	8/29 (27.6)	14/54 (25.9)	5/31 (16.1)	26/111 (23.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.76 [0.35, 1.66], 0.4942		1.61 [0.64, 4.04], 0.3123		1.08 [0.60, 1.94], 0.7946	
OR [95%-CI]; p-value	0.70 [0.25, 1.97], 0.4978		1.82 [0.59, 5.66], 0.2967		1.11 [0.52, 2.35], 0.7939	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.13], 0.5094		0.10 [-0.08, 0.27], 0.2710		0.02 [-0.11, 0.15], 0.7922	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5701		0.6003		0.5455	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	12/58 (20.7)	11/33 (33.3)	10/65 (15.4)	5/29 (17.2)	22/123 (17.9)	16/62 (25.8)
RR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1803		0.89 [0.33, 2.38], 0.8198		0.69 [0.39, 1.22], 0.2051	
OR [95%-CI]; p-value	0.52 [0.20, 1.37], 0.1821		0.87 [0.27, 2.83], 0.8204		0.63 [0.30, 1.30], 0.2081	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.07], 0.1960		-0.02 [-0.18, 0.14], 0.8234		-0.08 [-0.21, 0.05], 0.2262	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	10/54 (18.5)	9/31 (29.0)	18/111 (16.2)	18/60 (30.0)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		0.64 [0.29, 1.40], 0.2615		0.54 [0.30, 0.96], 0.0353	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		0.56 [0.20, 1.57], 0.2627		0.45 [0.21, 0.95], 0.0349	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		-0.11 [-0.30, 0.09], 0.2792		-0.14 [-0.27, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8883		0.0491		0.1376	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	6/33 (18.2)	9/65 (13.8)	1/29 (3.4)	15/123 (12.2)	7/62 (11.3)
RR [95%-CI]; p-value	0.57 [0.20, 1.62], 0.2915		4.02 [0.53, 30.24], 0.1772		1.08 [0.46, 2.51], 0.8579	
OR [95%-CI]; p-value	0.52 [0.15, 1.76], 0.2881		4.50 [0.54, 37.31], 0.1310		1.09 [0.42, 2.83], 0.8576	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3159		0.10 [-0.00, 0.21], 0.0570		0.01 [-0.09, 0.11], 0.8560	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	5/29 (17.2)	4/54 (7.4)	6/31 (19.4)	9/111 (8.1)	11/60 (18.3)
RR [95%-CI]; p-value	0.51 [0.16, 1.62], 0.2520		0.38 [0.12, 1.25], 0.1123		0.44 [0.19, 1.01], 0.0520	
OR [95%-CI]; p-value	0.46 [0.12, 1.75], 0.2467		0.33 [0.09, 1.29], 0.0998		0.39 [0.15, 1.01], 0.0471	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2869		-0.12 [-0.28, 0.04], 0.1324		-0.10 [-0.21, 0.01], 0.0692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3444		0.4873		0.2986	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	4/33 (12.1)	3/65 (4.6)	2/29 (6.9)	4/123 (3.3)	6/62 (9.7)
RR [95%-CI]; p-value	0.14 [0.02, 1.22], 0.0753		0.67 [0.12, 3.79], 0.6500		0.34 [0.10, 1.15], 0.0817	
OR [95%-CI]; p-value	0.13 [0.01, 1.19], 0.0364		0.65 [0.10, 4.14], 0.6490		0.31 [0.09, 1.16], 0.0681	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0797		-0.02 [-0.13, 0.08], 0.6714		-0.06 [-0.14, 0.02], 0.1154	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	3/29 (10.3)	2/54 (3.7)	0/31 (0.0)	5/111 (4.5)	3/60 (5.0)
RR [95%-CI]; p-value	0.51 [0.11, 2.37], 0.3887		2.33 [0.11, 50.15], 0.5883		0.90 [0.22, 3.64], 0.8836	
OR [95%-CI]; p-value	0.48 [0.09, 2.55], 0.3818		2.38 [0.10, 54.59], 0.5753		0.90 [0.21, 3.89], 0.8836	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4259		0.02 [-0.05, 0.09], 0.5337		-0.00 [-0.07, 0.06], 0.8853	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5765		0.3627		0.8559	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	6/33 (18.2)	11/65 (16.9)	3/29 (10.3)	18/123 (14.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.66 [0.24, 1.81], 0.4234		1.64 [0.49, 5.43], 0.4212		1.01 [0.48, 2.11], 0.9829	
OR [95%-CI]; p-value	0.62 [0.19, 2.02], 0.4230		1.77 [0.45, 6.88], 0.4080		1.01 [0.42, 2.40], 0.9829	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4426		0.07 [-0.08, 0.21], 0.3690		0.00 [-0.11, 0.11], 0.9829	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	4/29 (13.8)	2/54 (3.7)	2/31 (6.5)	10/111 (9.0)	6/60 (10.0)
RR [95%-CI]; p-value	1.02 [0.33, 3.10], 0.9756		0.57 [0.09, 3.88], 0.5689		0.90 [0.34, 2.36], 0.8317	
OR [95%-CI]; p-value	1.02 [0.28, 3.72], 0.9756		0.56 [0.07, 4.17], 0.5647		0.89 [0.31, 2.58], 0.8318	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9755		-0.03 [-0.13, 0.07], 0.5905		-0.01 [-0.10, 0.08], 0.8341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5878		0.6564		0.9938	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	2/58 (3.4)	4/33 (12.1)	6/65 (9.2)	2/29 (6.9)	8/123 (6.5)	6/62 (9.7)
RR [95%-CI]; p-value	0.28 [0.06, 1.47], 0.1336		1.34 [0.29, 6.24], 0.7105		0.67 [0.24, 1.85], 0.4422	
OR [95%-CI]; p-value	0.26 [0.04, 1.50], 0.1090		1.37 [0.26, 7.25], 0.7080		0.65 [0.21, 1.96], 0.4411	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1596		0.02 [-0.09, 0.14], 0.6933		-0.03 [-0.12, 0.05], 0.4671	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	4/29 (13.8)	6/54 (11.1)	4/31 (12.9)	10/111 (9.0)	8/60 (13.3)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3127		0.86 [0.26, 2.82], 0.8047		0.68 [0.28, 1.62], 0.3799	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3065		0.84 [0.22, 3.26], 0.8050		0.64 [0.24, 1.73], 0.3792	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3495		-0.02 [-0.16, 0.13], 0.8083		-0.04 [-0.14, 0.06], 0.4022	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.4040		0.8901		0.4786	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	5/58 (8.6)	5/33 (15.2)	4/65 (6.2)	4/29 (13.8)	9/123 (7.3)	9/62 (14.5)
RR [95%-CI]; p-value	0.57 [0.18, 1.82], 0.3422		0.45 [0.12, 1.66], 0.2290		0.50 [0.21, 1.21], 0.1236	
OR [95%-CI]; p-value	0.53 [0.14, 1.98], 0.3382		0.41 [0.09, 1.77], 0.2202		0.46 [0.17, 1.24], 0.1189	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.08], 0.3676		-0.08 [-0.21, 0.06], 0.2794		-0.07 [-0.17, 0.03], 0.1542	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	3/29 (10.3)	2/54 (3.7)	3/31 (9.7)	9/111 (8.1)	6/60 (10.0)
RR [95%-CI]; p-value	1.19 [0.33, 4.25], 0.7922		0.38 [0.07, 2.17], 0.2776		0.81 [0.30, 2.17], 0.6762	
OR [95%-CI]; p-value	1.21 [0.29, 5.09], 0.7912		0.36 [0.06, 2.28], 0.2599		0.79 [0.27, 2.35], 0.6764	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7861		-0.06 [-0.18, 0.06], 0.3112		-0.02 [-0.11, 0.07], 0.6847	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_1_m_soc_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8169		0.5475		0.2323	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	4/33 (12.1)	5/65 (7.7)	0/29 (0.0)	6/123 (4.9)	4/62 (6.5)
RR [95%-CI]; p-value	0.14 [0.02, 1.22], 0.0753		4.54 [0.26, 80.39], 0.3024		0.76 [0.22, 2.58], 0.6554	
OR [95%-CI]; p-value	0.13 [0.01, 1.19], 0.0364		4.83 [0.26, 91.49], 0.2485		0.74 [0.20, 2.74], 0.6550	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0797		0.06 [-0.02, 0.14], 0.1407		-0.02 [-0.09, 0.06], 0.6685	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	8/29 (27.6)	1/54 (1.9)	0/31 (0.0)	4/111 (3.6)	8/60 (13.3)
RR [95%-CI]; p-value	0.19 [0.05, 0.67], 0.0094		1.17 [0.04, 33.80], 0.9285		0.27 [0.08, 0.86], 0.0269	
OR [95%-CI]; p-value	0.15 [0.04, 0.60], 0.0034		1.17 [0.04, 35.89], 0.9284		0.24 [0.07, 0.84], 0.0174	
RD [95%-CI]; p-value	-0.22 [-0.40, -0.05], 0.0113		0.00 [-0.05, 0.06], 0.9269		-0.10 [-0.19, -0.00], 0.0398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_3_m_pt_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.2599		0.4048		0.7658	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	5/33 (15.2)	4/65 (6.2)	0/29 (0.0)	5/123 (4.1)	5/62 (8.1)
RR [95%-CI]; p-value	0.11 [0.01, 0.93], 0.0429		3.63 [0.20, 66.49], 0.3847		0.50 [0.15, 1.68], 0.2637	
OR [95%-CI]; p-value	0.10 [0.01, 0.88], 0.0131		3.80 [0.19, 74.36], 0.3456		0.48 [0.13, 1.74], 0.2561	
RD [95%-CI]; p-value	-0.13 [-0.26, -0.01], 0.0380		0.04 [-0.03, 0.12], 0.2421		-0.04 [-0.12, 0.04], 0.3038	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	3/29 (10.3)	3/54 (5.6)	2/31 (6.5)	6/111 (5.4)	5/60 (8.3)
RR [95%-CI]; p-value	0.51 [0.11, 2.37], 0.3887		0.86 [0.15, 4.88], 0.8658		0.65 [0.21, 2.04], 0.4585	
OR [95%-CI]; p-value	0.48 [0.09, 2.55], 0.3818		0.85 [0.13, 5.40], 0.8658		0.63 [0.18, 2.15], 0.4564	
RD [95%-CI]; p-value	-0.05 [-0.18, 0.07], 0.4259		-0.01 [-0.11, 0.10], 0.8683		-0.03 [-0.11, 0.05], 0.4819	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_3_m_pt_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.7390		0.4617		0.3352	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	2/33 (6.1)	2/65 (3.1)	4/29 (13.8)	5/123 (4.1)	6/62 (9.7)
RR [95%-CI]; p-value	0.85 [0.15, 4.85], 0.8581		0.22 [0.04, 1.15], 0.0730		0.42 [0.13, 1.32], 0.1383	
OR [95%-CI]; p-value	0.85 [0.13, 5.34], 0.8581		0.20 [0.03, 1.15], 0.0496		0.40 [0.12, 1.35], 0.1276	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8609		-0.11 [-0.24, 0.03], 0.1125		-0.06 [-0.14, 0.03], 0.1768	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	2/29 (6.9)	2/54 (3.7)	2/31 (6.5)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	1.27 [0.26, 6.16], 0.7651		0.57 [0.09, 3.88], 0.5689		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	1.30 [0.24, 7.14], 0.7637		0.56 [0.07, 4.17], 0.5647		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7552		-0.03 [-0.13, 0.07], 0.5905		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_3_m_pt_ae10pct_ckd_pp.sas using SAS 9.4

Table 12.4.8.1.1.s5.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.7111		0.8109		0.4960	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	0/33 (0.0)	1/65 (1.5)	1/29 (3.4)	2/123 (1.6)	1/62 (1.6)
RR [95%-CI]; p-value	1.16 [0.04, 33.52], 0.9331		0.45 [0.03, 6.89], 0.5633		1.01 [0.09, 10.90], 0.9947	
OR [95%-CI]; p-value	1.16 [0.04, 35.46], 0.9330		0.44 [0.03, 7.25], 0.5534		1.01 [0.09, 11.34], 0.9947	
RD [95%-CI]; p-value	0.00 [-0.05, 0.06], 0.9317		-0.02 [-0.09, 0.05], 0.6073		0.00 [-0.04, 0.04], 0.9947	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	1/29 (3.4)	1/54 (1.9)	2/31 (6.5)	2/111 (1.8)	3/60 (5.0)
RR [95%-CI]; p-value	0.51 [0.03, 7.84], 0.6283		0.29 [0.03, 3.04], 0.2998		0.36 [0.06, 2.10], 0.2561	
OR [95%-CI]; p-value	0.50 [0.03, 8.29], 0.6222		0.27 [0.02, 3.15], 0.2686		0.35 [0.06, 2.15], 0.2361	
RD [95%-CI]; p-value	-0.02 [-0.09, 0.06], 0.6565		-0.05 [-0.14, 0.05], 0.3358		-0.03 [-0.09, 0.03], 0.2997	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_8_1_1_m_soc_sae5pct_ckd_pp.sas using SAS 9.4

Table 12.4.8.1.2.s5.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_8_1_2_m_pt_sae5pct_ckd_pp.sas using SAS 9.4

Table 12.4.5.1.1.s5.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_5_1_1_m_soc_aeg35pct_ckd_pp.sas using SAS 9.4

Table 12.4.5.1.2.s5.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_5_1_2_m_pt_aeg35pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.2944		0.2435		0.1577	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	13/58 (22.4)	9/33 (27.3)	15/65 (23.1)	2/29 (6.9)	28/123 (22.8)	11/62 (17.7)
RR [95%-CI]; p-value	0.82 [0.39, 1.71], 0.6006		3.35 [0.82, 13.69], 0.0929		1.28 [0.69, 2.40], 0.4359	
OR [95%-CI]; p-value	0.77 [0.29, 2.06], 0.6027		4.05 [0.86, 19.04], 0.0598		1.37 [0.63, 2.97], 0.4292	
RD [95%-CI]; p-value	-0.05 [-0.23, 0.14], 0.6087		0.16 [0.02, 0.30], 0.0214		0.05 [-0.07, 0.17], 0.4142	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	8/54 (14.8)	4/31 (12.9)	16/111 (14.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		1.15 [0.38, 3.50], 0.8083		0.67 [0.34, 1.29], 0.2269	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		1.17 [0.32, 4.27], 0.8075		0.61 [0.27, 1.37], 0.2278	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		0.02 [-0.13, 0.17], 0.8045		-0.07 [-0.20, 0.05], 0.2479	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.5656		0.4841		0.4231	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	9/58 (15.5)	8/33 (24.2)	9/65 (13.8)	3/29 (10.3)	18/123 (14.6)	11/62 (17.7)
RR [95%-CI]; p-value	0.64 [0.27, 1.50], 0.3042		1.34 [0.39, 4.58], 0.6426		0.82 [0.42, 1.64], 0.5817	
OR [95%-CI]; p-value	0.57 [0.20, 1.67], 0.3046		1.39 [0.35, 5.58], 0.6385		0.79 [0.35, 1.81], 0.5831	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.09], 0.3240		0.04 [-0.10, 0.17], 0.6216		-0.03 [-0.14, 0.08], 0.5924	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	7/29 (24.1)	5/54 (9.3)	4/31 (12.9)	11/111 (9.9)	11/60 (18.3)
RR [95%-CI]; p-value	0.44 [0.16, 1.18], 0.1020		0.72 [0.21, 2.48], 0.5994		0.54 [0.25, 1.17], 0.1195	
OR [95%-CI]; p-value	0.37 [0.11, 1.23], 0.0957		0.69 [0.17, 2.78], 0.5992		0.49 [0.20, 1.21], 0.1164	
RD [95%-CI]; p-value	-0.14 [-0.31, 0.04], 0.1273		-0.04 [-0.18, 0.10], 0.6127		-0.08 [-0.20, 0.03], 0.1425	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.9095		0.2897		0.4332	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	16/58 (27.6)	9/33 (27.3)	18/65 (27.7)	6/29 (20.7)	34/123 (27.6)	15/62 (24.2)
RR [95%-CI]; p-value	1.01 [0.50, 2.03], 0.9743		1.34 [0.59, 3.02], 0.4826		1.14 [0.68, 1.93], 0.6190	
OR [95%-CI]; p-value	1.02 [0.39, 2.65], 0.9743		1.47 [0.51, 4.20], 0.4720		1.20 [0.59, 2.42], 0.6158	
RD [95%-CI]; p-value	0.00 [-0.19, 0.19], 0.9743		0.07 [-0.11, 0.25], 0.4538		0.03 [-0.10, 0.17], 0.6105	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	15/57 (26.3)	8/29 (27.6)	10/54 (18.5)	8/31 (25.8)	25/111 (22.5)	16/60 (26.7)
RR [95%-CI]; p-value	0.95 [0.46, 1.98], 0.8996		0.72 [0.32, 1.63], 0.4266		0.84 [0.49, 1.45], 0.5423	
OR [95%-CI]; p-value	0.94 [0.34, 2.56], 0.8999		0.65 [0.23, 1.88], 0.4286		0.80 [0.39, 1.65], 0.5447	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9003		-0.07 [-0.26, 0.11], 0.4416		-0.04 [-0.18, 0.09], 0.5510	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.6500		0.8707		0.5916	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	5/58 (8.6)	3/33 (9.1)	4/65 (6.2)	1/29 (3.4)	9/123 (7.3)	4/62 (6.5)
RR [95%-CI]; p-value	0.95 [0.24, 3.72], 0.9393		1.78 [0.21, 15.28], 0.5970		1.13 [0.36, 3.54], 0.8283	
OR [95%-CI]; p-value	0.94 [0.21, 4.23], 0.9393		1.84 [0.20, 17.19], 0.5893		1.14 [0.34, 3.88], 0.8279	
RD [95%-CI]; p-value	-0.00 [-0.13, 0.12], 0.9397		0.03 [-0.06, 0.12], 0.5488		0.01 [-0.07, 0.09], 0.8246	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	6/57 (10.5)	2/29 (6.9)	4/54 (7.4)	1/31 (3.2)	10/111 (9.0)	3/60 (5.0)
RR [95%-CI]; p-value	1.53 [0.33, 7.10], 0.5896		2.30 [0.27, 19.64], 0.4478		1.80 [0.52, 6.30], 0.3564	
OR [95%-CI]; p-value	1.59 [0.30, 8.41], 0.5838		2.40 [0.26, 22.49], 0.4303		1.88 [0.50, 7.12], 0.3452	
RD [95%-CI]; p-value	0.04 [-0.09, 0.16], 0.5594		0.04 [-0.05, 0.14], 0.3809		0.04 [-0.04, 0.12], 0.3054	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.8839		0.2850		0.5047	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	5/33 (15.2)	6/65 (9.2)	1/29 (3.4)	13/123 (10.6)	6/62 (9.7)
RR [95%-CI]; p-value	0.80 [0.27, 2.31], 0.6755		2.68 [0.34, 21.24], 0.3515		1.09 [0.44, 2.73], 0.8507	
OR [95%-CI]; p-value	0.77 [0.22, 2.65], 0.6761		2.85 [0.33, 24.80], 0.3240		1.10 [0.40, 3.06], 0.8504	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.12], 0.6837		0.06 [-0.04, 0.15], 0.2415		0.01 [-0.08, 0.10], 0.8485	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	5/29 (17.2)	5/54 (9.3)	4/31 (12.9)	12/111 (10.8)	9/60 (15.0)
RR [95%-CI]; p-value	0.71 [0.25, 2.05], 0.5293		0.72 [0.21, 2.48], 0.5994		0.72 [0.32, 1.61], 0.4253	
OR [95%-CI]; p-value	0.67 [0.19, 2.34], 0.5302		0.69 [0.17, 2.78], 0.5992		0.69 [0.27, 1.74], 0.4257	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.11], 0.5478		-0.04 [-0.18, 0.10], 0.6127		-0.04 [-0.15, 0.07], 0.4439	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5859		0.0578		0.0694	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	11/58 (19.0)	11/33 (33.3)	7/65 (10.8)	7/29 (24.1)	18/123 (14.6)	18/62 (29.0)
RR [95%-CI]; p-value	0.57 [0.28, 1.17], 0.1238		0.45 [0.17, 1.16], 0.0965		0.50 [0.28, 0.90], 0.0201	
OR [95%-CI]; p-value	0.47 [0.18, 1.24], 0.1238		0.38 [0.12, 1.21], 0.0927		0.42 [0.20, 0.88], 0.0195	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.05], 0.1380		-0.13 [-0.31, 0.04], 0.1299		-0.14 [-0.27, -0.01], 0.0288	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	12/57 (21.1)	8/29 (27.6)	14/54 (25.9)	5/31 (16.1)	26/111 (23.4)	13/60 (21.7)
RR [95%-CI]; p-value	0.76 [0.35, 1.66], 0.4942		1.61 [0.64, 4.04], 0.3123		1.08 [0.60, 1.94], 0.7946	
OR [95%-CI]; p-value	0.70 [0.25, 1.97], 0.4978		1.82 [0.59, 5.66], 0.2967		1.11 [0.52, 2.35], 0.7939	
RD [95%-CI]; p-value	-0.07 [-0.26, 0.13], 0.5094		0.10 [-0.08, 0.27], 0.2710		0.02 [-0.11, 0.15], 0.7922	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
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Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.5701		0.6003		0.5455	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	12/58 (20.7)	11/33 (33.3)	10/65 (15.4)	5/29 (17.2)	22/123 (17.9)	16/62 (25.8)
RR [95%-CI]; p-value	0.62 [0.31, 1.25], 0.1803		0.89 [0.33, 2.38], 0.8198		0.69 [0.39, 1.22], 0.2051	
OR [95%-CI]; p-value	0.52 [0.20, 1.37], 0.1821		0.87 [0.27, 2.83], 0.8204		0.63 [0.30, 1.30], 0.2081	
RD [95%-CI]; p-value	-0.13 [-0.32, 0.07], 0.1960		-0.02 [-0.18, 0.14], 0.8234		-0.08 [-0.21, 0.05], 0.2262	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	9/29 (31.0)	10/54 (18.5)	9/31 (29.0)	18/111 (16.2)	18/60 (30.0)
RR [95%-CI]; p-value	0.45 [0.20, 1.05], 0.0644		0.64 [0.29, 1.40], 0.2615		0.54 [0.30, 0.96], 0.0353	
OR [95%-CI]; p-value	0.36 [0.12, 1.07], 0.0613		0.56 [0.20, 1.57], 0.2627		0.45 [0.21, 0.95], 0.0349	
RD [95%-CI]; p-value	-0.17 [-0.36, 0.02], 0.0811		-0.11 [-0.30, 0.09], 0.2792		-0.14 [-0.27, -0.00], 0.0449	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8883		0.0491		0.1376	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	6/33 (18.2)	9/65 (13.8)	1/29 (3.4)	15/123 (12.2)	7/62 (11.3)
RR [95%-CI]; p-value	0.57 [0.20, 1.62], 0.2915		4.02 [0.53, 30.24], 0.1772		1.08 [0.46, 2.51], 0.8579	
OR [95%-CI]; p-value	0.52 [0.15, 1.76], 0.2881		4.50 [0.54, 37.31], 0.1310		1.09 [0.42, 2.83], 0.8576	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3159		0.10 [-0.00, 0.21], 0.0570		0.01 [-0.09, 0.11], 0.8560	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	5/57 (8.8)	5/29 (17.2)	4/54 (7.4)	6/31 (19.4)	9/111 (8.1)	11/60 (18.3)
RR [95%-CI]; p-value	0.51 [0.16, 1.62], 0.2520		0.38 [0.12, 1.25], 0.1123		0.44 [0.19, 1.01], 0.0520	
OR [95%-CI]; p-value	0.46 [0.12, 1.75], 0.2467		0.33 [0.09, 1.29], 0.0998		0.39 [0.15, 1.01], 0.0471	
RD [95%-CI]; p-value	-0.08 [-0.24, 0.07], 0.2869		-0.12 [-0.28, 0.04], 0.1324		-0.10 [-0.21, 0.01], 0.0692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.5765		0.3627		0.8559	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	7/58 (12.1)	6/33 (18.2)	11/65 (16.9)	3/29 (10.3)	18/123 (14.6)	9/62 (14.5)
RR [95%-CI]; p-value	0.66 [0.24, 1.81], 0.4234		1.64 [0.49, 5.43], 0.4212		1.01 [0.48, 2.11], 0.9829	
OR [95%-CI]; p-value	0.62 [0.19, 2.02], 0.4230		1.77 [0.45, 6.88], 0.4080		1.01 [0.42, 2.40], 0.9829	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.09], 0.4426		0.07 [-0.08, 0.21], 0.3690		0.00 [-0.11, 0.11], 0.9829	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	4/29 (13.8)	2/54 (3.7)	2/31 (6.5)	10/111 (9.0)	6/60 (10.0)
RR [95%-CI]; p-value	1.02 [0.33, 3.10], 0.9756		0.57 [0.09, 3.88], 0.5689		0.90 [0.34, 2.36], 0.8317	
OR [95%-CI]; p-value	1.02 [0.28, 3.72], 0.9756		0.56 [0.07, 4.17], 0.5647		0.89 [0.31, 2.58], 0.8318	
RD [95%-CI]; p-value	0.00 [-0.15, 0.16], 0.9755		-0.03 [-0.13, 0.07], 0.5905		-0.01 [-0.10, 0.08], 0.8341	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.5878		0.6564		0.9938	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	2/58 (3.4)	4/33 (12.1)	6/65 (9.2)	2/29 (6.9)	8/123 (6.5)	6/62 (9.7)
RR [95%-CI]; p-value	0.28 [0.06, 1.47], 0.1336		1.34 [0.29, 6.24], 0.7105		0.67 [0.24, 1.85], 0.4422	
OR [95%-CI]; p-value	0.26 [0.04, 1.50], 0.1090		1.37 [0.26, 7.25], 0.7080		0.65 [0.21, 1.96], 0.4411	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1596		0.02 [-0.09, 0.14], 0.6933		-0.03 [-0.12, 0.05], 0.4671	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	4/29 (13.8)	6/54 (11.1)	4/31 (12.9)	10/111 (9.0)	8/60 (13.3)
RR [95%-CI]; p-value	0.51 [0.14, 1.89], 0.3127		0.86 [0.26, 2.82], 0.8047		0.68 [0.28, 1.62], 0.3799	
OR [95%-CI]; p-value	0.47 [0.11, 2.04], 0.3065		0.84 [0.22, 3.26], 0.8050		0.64 [0.24, 1.73], 0.3792	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.07], 0.3495		-0.02 [-0.16, 0.13], 0.8083		-0.04 [-0.14, 0.06], 0.4022	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.4040		0.8901		0.4786	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	5/58 (8.6)	5/33 (15.2)	4/65 (6.2)	4/29 (13.8)	9/123 (7.3)	9/62 (14.5)
RR [95%-CI]; p-value	0.57 [0.18, 1.82], 0.3422		0.45 [0.12, 1.66], 0.2290		0.50 [0.21, 1.21], 0.1236	
OR [95%-CI]; p-value	0.53 [0.14, 1.98], 0.3382		0.41 [0.09, 1.77], 0.2202		0.46 [0.17, 1.24], 0.1189	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.08], 0.3676		-0.08 [-0.21, 0.06], 0.2794		-0.07 [-0.17, 0.03], 0.1542	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	3/29 (10.3)	2/54 (3.7)	3/31 (9.7)	9/111 (8.1)	6/60 (10.0)
RR [95%-CI]; p-value	1.19 [0.33, 4.25], 0.7922		0.38 [0.07, 2.17], 0.2776		0.81 [0.30, 2.17], 0.6762	
OR [95%-CI]; p-value	1.21 [0.29, 5.09], 0.7912		0.36 [0.06, 2.28], 0.2599		0.79 [0.27, 2.35], 0.6764	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7861		-0.06 [-0.18, 0.06], 0.3112		-0.02 [-0.11, 0.07], 0.6847	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_2_m_soc_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.4.s5.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.8169		0.5475		0.2323	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	1/58 (1.7)	4/33 (12.1)	5/65 (7.7)	0/29 (0.0)	6/123 (4.9)	4/62 (6.5)
RR [95%-CI]; p-value	0.14 [0.02, 1.22], 0.0753		4.54 [0.26, 80.39], 0.3024		0.76 [0.22, 2.58], 0.6554	
OR [95%-CI]; p-value	0.13 [0.01, 1.19], 0.0364		4.83 [0.26, 91.49], 0.2485		0.74 [0.20, 2.74], 0.6550	
RD [95%-CI]; p-value	-0.10 [-0.22, 0.01], 0.0797		0.06 [-0.02, 0.14], 0.1407		-0.02 [-0.09, 0.06], 0.6685	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	8/29 (27.6)	1/54 (1.9)	0/31 (0.0)	4/111 (3.6)	8/60 (13.3)
RR [95%-CI]; p-value	0.19 [0.05, 0.67], 0.0094		1.17 [0.04, 33.80], 0.9285		0.27 [0.08, 0.86], 0.0269	
OR [95%-CI]; p-value	0.15 [0.04, 0.60], 0.0034		1.17 [0.04, 35.89], 0.9284		0.24 [0.07, 0.84], 0.0174	
RD [95%-CI]; p-value	-0.22 [-0.40, -0.05], 0.0113		0.00 [-0.05, 0.06], 0.9269		-0.10 [-0.19, -0.00], 0.0398	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_4_m_pt_ae1pct_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.1790		0.7489		0.4668	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	2/33 (6.1)	2/65 (3.1)	1/29 (3.4)	5/123 (4.1)	3/62 (4.8)
RR [95%-CI]; p-value	0.85 [0.15, 4.85], 0.8581		0.89 [0.08, 9.45], 0.9246		0.84 [0.21, 3.40], 0.8071	
OR [95%-CI]; p-value	0.85 [0.13, 5.34], 0.8581		0.89 [0.08, 10.21], 0.9246		0.83 [0.19, 3.61], 0.8071	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8609		-0.00 [-0.08, 0.07], 0.9262		-0.01 [-0.07, 0.06], 0.8121	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	8/57 (14.0)	0/29 (0.0)	4/54 (7.4)	4/31 (12.9)	12/111 (10.8)	4/60 (6.7)
RR [95%-CI]; p-value	8.28 [0.49, 139.25], 0.1421		0.57 [0.15, 2.14], 0.4076		1.62 [0.55, 4.81], 0.3834	
OR [95%-CI]; p-value	9.47 [0.52, 171.03], 0.0676		0.54 [0.13, 2.33], 0.4036		1.70 [0.52, 5.51], 0.3745	
RD [95%-CI]; p-value	0.12 [0.02, 0.22], 0.0172		-0.05 [-0.19, 0.08], 0.4322		0.04 [-0.04, 0.13], 0.3425	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8217		NA		0.7710	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	0/33 (0.0)	0/65 (0.0)	0/29 (0.0)	0/123 (0.0)	0/62 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	0/29 (0.0)	0/54 (0.0)	0/31 (0.0)	1/111 (0.9)	0/60 (0.0)
RR [95%-CI]; p-value	1.04 [0.04, 29.96], 0.9840		NA		1.09 [0.04, 32.03], 0.9601	
OR [95%-CI]; p-value	1.04 [0.03, 31.80], 0.9840		NA		1.09 [0.04, 32.99], 0.9601	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9839		NA		0.00 [-0.03, 0.03], 0.9596	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2073		0.7489		0.5297	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	2/33 (6.1)	2/65 (3.1)	1/29 (3.4)	5/123 (4.1)	3/62 (4.8)
RR [95%-CI]; p-value	0.85 [0.15, 4.85], 0.8581		0.89 [0.08, 9.45], 0.9246		0.84 [0.21, 3.40], 0.8071	
OR [95%-CI]; p-value	0.85 [0.13, 5.34], 0.8581		0.89 [0.08, 10.21], 0.9246		0.83 [0.19, 3.61], 0.8071	
RD [95%-CI]; p-value	-0.01 [-0.11, 0.09], 0.8609		-0.00 [-0.08, 0.07], 0.9262		-0.01 [-0.07, 0.06], 0.8121	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	0/29 (0.0)	4/54 (7.4)	4/31 (12.9)	11/111 (9.9)	4/60 (6.7)
RR [95%-CI]; p-value	7.25 [0.43, 123.33], 0.1709		0.57 [0.15, 2.14], 0.4076		1.49 [0.49, 4.47], 0.4802	
OR [95%-CI]; p-value	8.12 [0.44, 148.36], 0.0972		0.54 [0.13, 2.33], 0.4036		1.54 [0.47, 5.06], 0.4743	
RD [95%-CI]; p-value	0.11 [0.01, 0.20], 0.0326		-0.05 [-0.19, 0.08], 0.4322		0.03 [-0.05, 0.12], 0.4498	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.6034		0.8636		0.6851	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	2/58 (3.4)	1/33 (3.0)	1/65 (1.5)	0/29 (0.0)	3/123 (2.4)	1/62 (1.6)
RR [95%-CI]; p-value	1.14 [0.11, 12.08], 0.9146		0.91 [0.03, 26.31], 0.9550		1.51 [0.16, 14.24], 0.7178	
OR [95%-CI]; p-value	1.14 [0.10, 13.10], 0.9145		0.91 [0.03, 27.79], 0.9550		1.53 [0.16, 14.97], 0.7154	
RD [95%-CI]; p-value	0.00 [-0.07, 0.08], 0.9130		-0.00 [-0.06, 0.05], 0.9558		0.01 [-0.03, 0.05], 0.6968	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	0/29 (0.0)	0/54 (0.0)	0/31 (0.0)	3/111 (2.7)	0/60 (0.0)
RR [95%-CI]; p-value	3.11 [0.16, 59.97], 0.4532		NA		3.27 [0.17, 64.22], 0.4354	
OR [95%-CI]; p-value	3.22 [0.16, 66.54], 0.4246		NA		3.33 [0.16, 67.66], 0.4063	
RD [95%-CI]; p-value	0.04 [-0.04, 0.11], 0.3470		NA		0.02 [-0.02, 0.06], 0.3309	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.4529		0.9744		0.5376	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	7/33 (21.2)	6/65 (9.2)	3/29 (10.3)	12/123 (9.8)	10/62 (16.1)
RR [95%-CI]; p-value	0.49 [0.18, 1.33], 0.1606		0.89 [0.24, 3.32], 0.8651		0.60 [0.28, 1.32], 0.2075	
OR [95%-CI]; p-value	0.43 [0.13, 1.41], 0.1544		0.88 [0.20, 3.80], 0.8654		0.56 [0.23, 1.38], 0.2062	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.05], 0.1831		-0.01 [-0.14, 0.12], 0.8679		-0.06 [-0.17, 0.04], 0.2365	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	4/57 (7.0)	2/29 (6.9)	3/54 (5.6)	2/31 (6.5)	7/111 (6.3)	4/60 (6.7)
RR [95%-CI]; p-value	1.02 [0.20, 5.23], 0.9834		0.86 [0.15, 4.88], 0.8658		0.95 [0.29, 3.10], 0.9269	
OR [95%-CI]; p-value	1.02 [0.18, 5.92], 0.9834		0.85 [0.13, 5.40], 0.8658		0.94 [0.26, 3.36], 0.9270	
RD [95%-CI]; p-value	0.00 [-0.11, 0.11], 0.9833		-0.01 [-0.11, 0.10], 0.8683		-0.00 [-0.08, 0.07], 0.9275	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8217		0.6641		0.4876	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	0/58 (0.0)	0/33 (0.0)	1/65 (1.5)	1/29 (3.4)	1/123 (0.8)	1/62 (1.6)
RR [95%-CI]; p-value	NA		0.45 [0.03, 6.89], 0.5633		0.50 [0.03, 7.92], 0.6260	
OR [95%-CI]; p-value	NA		0.44 [0.03, 7.25], 0.5534		0.50 [0.03, 8.13], 0.6195	
RD [95%-CI]; p-value	NA		-0.02 [-0.09, 0.05], 0.6073		-0.01 [-0.04, 0.03], 0.6555	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	0/29 (0.0)	1/54 (1.9)	0/31 (0.0)	2/111 (1.8)	0/60 (0.0)
RR [95%-CI]; p-value	1.04 [0.04, 29.96], 0.9840		1.17 [0.04, 33.80], 0.9285		2.18 [0.10, 47.58], 0.6203	
OR [95%-CI]; p-value	1.04 [0.03, 31.80], 0.9840		1.17 [0.04, 35.89], 0.9284		2.20 [0.10, 49.61], 0.6106	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9839		0.00 [-0.05, 0.06], 0.9269		0.01 [-0.02, 0.04], 0.5700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.6611		0.7093		0.8848	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	6/58 (10.3)	7/33 (21.2)	6/65 (9.2)	3/29 (10.3)	12/123 (9.8)	10/62 (16.1)
RR [95%-CI]; p-value	0.49 [0.18, 1.33], 0.1606		0.89 [0.24, 3.32], 0.8651		0.60 [0.28, 1.32], 0.2075	
OR [95%-CI]; p-value	0.43 [0.13, 1.41], 0.1544		0.88 [0.20, 3.80], 0.8654		0.56 [0.23, 1.38], 0.2062	
RD [95%-CI]; p-value	-0.11 [-0.27, 0.05], 0.1831		-0.01 [-0.14, 0.12], 0.8679		-0.06 [-0.17, 0.04], 0.2365	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	3/57 (5.3)	2/29 (6.9)	2/54 (3.7)	2/31 (6.5)	5/111 (4.5)	4/60 (6.7)
RR [95%-CI]; p-value	0.76 [0.13, 4.32], 0.7598		0.57 [0.09, 3.88], 0.5689		0.68 [0.19, 2.42], 0.5473	
OR [95%-CI]; p-value	0.75 [0.12, 4.76], 0.7596		0.56 [0.07, 4.17], 0.5647		0.66 [0.17, 2.56], 0.5457	
RD [95%-CI]; p-value	-0.02 [-0.13, 0.09], 0.7688		-0.03 [-0.13, 0.07], 0.5905		-0.02 [-0.10, 0.05], 0.5667	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s5.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.5974		0.8983		0.9395	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	3/58 (5.2)	0/33 (0.0)	2/65 (3.1)	1/29 (3.4)	5/123 (4.1)	1/62 (1.6)
RR [95%-CI]; p-value	3.47 [0.18, 67.11], 0.4111		0.89 [0.08, 9.45], 0.9246		2.52 [0.30, 21.11], 0.3939	
OR [95%-CI]; p-value	3.60 [0.17, 74.13], 0.3766		0.89 [0.08, 10.21], 0.9246		2.58 [0.30, 22.62], 0.3741	
RD [95%-CI]; p-value	0.04 [-0.03, 0.11], 0.3045		-0.00 [-0.08, 0.07], 0.9262		0.02 [-0.02, 0.07], 0.3057	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	1/57 (1.8)	0/29 (0.0)	1/54 (1.9)	0/31 (0.0)	2/111 (1.8)	0/60 (0.0)
RR [95%-CI]; p-value	1.04 [0.04, 29.96], 0.9840		1.17 [0.04, 33.80], 0.9285		2.18 [0.10, 47.58], 0.6203	
OR [95%-CI]; p-value	1.04 [0.03, 31.80], 0.9840		1.17 [0.04, 35.89], 0.9284		2.20 [0.10, 49.61], 0.6106	
RD [95%-CI]; p-value	0.00 [-0.06, 0.06], 0.9839		0.00 [-0.05, 0.06], 0.9269		0.01 [-0.02, 0.04], 0.5700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_7_m_pt_smq_ckd_pp.sas using SAS 9.4

Table 12.4.4.1.6.s5.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.CKD Stage 3 vs 2.CKD Stage 4

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.2534		0.2986		0.0795	
1.CKD Stage 3	N1=58	N1=33	N1=65	N1=29	N1=123	N1=62
n/N1 (%)	9/58 (15.5)	7/33 (21.2)	16/65 (24.6)	3/29 (10.3)	25/123 (20.3)	10/62 (16.1)
RR [95%-CI]; p-value	0.73 [0.30, 1.78], 0.4914		2.38 [0.75, 7.54], 0.1405		1.26 [0.65, 2.45], 0.4967	
OR [95%-CI]; p-value	0.68 [0.23, 2.04], 0.4927		2.83 [0.75, 10.61], 0.1115		1.33 [0.59, 2.97], 0.4915	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.11], 0.5058		0.14 [-0.01, 0.30], 0.0666		0.04 [-0.07, 0.16], 0.4781	
2.CKD Stage 4	N2=57	N2=29	N2=54	N2=31	N2=111	N2=60
n/N2 (%)	7/57 (12.3)	10/29 (34.5)	7/54 (13.0)	4/31 (12.9)	14/111 (12.6)	14/60 (23.3)
RR [95%-CI]; p-value	0.36 [0.15, 0.84], 0.0181		1.00 [0.32, 3.16], 0.9937		0.54 [0.28, 1.06], 0.0723	
OR [95%-CI]; p-value	0.27 [0.09, 0.80], 0.0145		1.01 [0.27, 3.75], 0.9937		0.47 [0.21, 1.08], 0.0706	
RD [95%-CI]; p-value	-0.22 [-0.41, -0.03], 0.0240		0.00 [-0.15, 0.15], 0.9937		-0.11 [-0.23, 0.02], 0.0890	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
CKD: Chronic Kidney Disease
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s5_ckd_pp/T12_4_4_1_6_m_pt_adr_ckd_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.2449		0.1512		0.8843	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	25/36 (69.4)	19/23 (82.6)	30/48 (62.5)	7/16 (43.8)	55/84 (65.5)	26/39 (66.7)
RR [95%-CI]; p-value	0.84 [0.63, 1.12], 0.2351		1.43 [0.79, 2.60], 0.2418		0.98 [0.75, 1.29], 0.8963	
OR [95%-CI]; p-value	0.48 [0.13, 1.74], 0.2574		2.14 [0.68, 6.75], 0.1884		0.95 [0.42, 2.12], 0.8969	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.08], 0.2322		0.19 [-0.09, 0.47], 0.1878		-0.01 [-0.19, 0.17], 0.8966	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	33/42 (78.6)	16/22 (72.7)	20/37 (54.1)	17/23 (73.9)	53/79 (67.1)	33/45 (73.3)
RR [95%-CI]; p-value	1.08 [0.80, 1.46], 0.6144		0.73 [0.50, 1.07], 0.1099		0.91 [0.72, 1.16], 0.4566	
OR [95%-CI]; p-value	1.38 [0.42, 4.53], 0.6001		0.42 [0.13, 1.29], 0.1240		0.74 [0.33, 1.67], 0.4683	
RD [95%-CI]; p-value	0.06 [-0.17, 0.28], 0.6086		-0.20 [-0.44, 0.04], 0.1060		-0.06 [-0.23, 0.10], 0.4599	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	25/37 (67.6)	15/17 (88.2)	22/34 (64.7)	13/21 (61.9)	47/71 (66.2)	28/38 (73.7)
RR [95%-CI]; p-value	0.77 [0.58, 1.02], 0.0643		1.05 [0.69, 1.59], 0.8354		0.90 [0.70, 1.16], 0.4055	
OR [95%-CI]; p-value	0.28 [0.05, 1.42], 0.1075		1.13 [0.37, 3.48], 0.8338		0.70 [0.29, 1.68], 0.4214	
RD [95%-CI]; p-value	-0.21 [-0.42, 0.01], 0.0595		0.03 [-0.23, 0.29], 0.8344		-0.07 [-0.25, 0.10], 0.4099	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.6667		0.3978		0.2948	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	3/23 (13.0)	2/48 (4.2)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.64 [0.14, 2.90], 0.5615		0.67 [0.06, 6.87], 0.7334		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.61 [0.11, 3.30], 0.5594		0.65 [0.06, 7.71], 0.7328		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.05 [-0.21, 0.12], 0.5749		-0.02 [-0.15, 0.11], 0.7560		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	3/22 (13.6)	6/37 (16.2)	0/23 (0.0)	12/79 (15.2)	3/45 (6.7)
RR [95%-CI]; p-value	1.05 [0.29, 3.79], 0.9435		7.62 [0.45, 130.23], 0.1608		2.28 [0.68, 7.65], 0.1826	
OR [95%-CI]; p-value	1.06 [0.24, 4.70], 0.9434		8.90 [0.47, 167.57], 0.0846		2.51 [0.67, 9.41], 0.1617	
RD [95%-CI]; p-value	0.01 [-0.17, 0.18], 0.9431		0.14 [0.01, 0.27], 0.0369		0.09 [-0.02, 0.19], 0.1205	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	4/17 (23.5)	5/34 (14.7)	1/21 (4.8)	9/71 (12.7)	5/38 (13.2)
RR [95%-CI]; p-value	0.46 [0.13, 1.62], 0.2269		3.09 [0.39, 24.65], 0.2873		0.96 [0.35, 2.67], 0.9428	
OR [95%-CI]; p-value	0.39 [0.09, 1.81], 0.2217		3.45 [0.37, 31.79], 0.2505		0.96 [0.30, 3.09], 0.9429	
RD [95%-CI]; p-value	-0.13 [-0.35, 0.10], 0.2681		0.10 [-0.05, 0.25], 0.1935		-0.00 [-0.14, 0.13], 0.9432	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.2355		0.4177		0.1185	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	3/84 (3.6)	4/39 (10.3)
RR [95%-CI]; p-value	0.43 [0.08, 2.36], 0.3282		0.33 [0.02, 5.03], 0.4275		0.35 [0.08, 1.48], 0.1533	
OR [95%-CI]; p-value	0.39 [0.06, 2.55], 0.3138		0.32 [0.02, 5.42], 0.4068		0.32 [0.07, 1.52], 0.1364	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.08], 0.3489		-0.04 [-0.17, 0.08], 0.5146		-0.07 [-0.17, 0.04], 0.2040	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	0/22 (0.0)	2/37 (5.4)	1/23 (4.3)	8/79 (10.1)	1/45 (2.2)
RR [95%-CI]; p-value	6.43 [0.38, 109.94], 0.1990		1.24 [0.12, 12.95], 0.8555		4.56 [0.59, 35.27], 0.1463	
OR [95%-CI]; p-value	7.33 [0.39, 137.80], 0.1251		1.26 [0.11, 14.70], 0.8550		4.96 [0.60, 41.00], 0.1028	
RD [95%-CI]; p-value	0.12 [-0.00, 0.24], 0.0528		0.01 [-0.10, 0.12], 0.8515		0.08 [-0.00, 0.16], 0.0506	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	1/17 (5.9)	0/34 (0.0)	3/21 (14.3)	4/71 (5.6)	4/38 (10.5)
RR [95%-CI]; p-value	1.84 [0.22, 15.23], 0.5727		0.10 [0.01, 1.93], 0.1277		0.54 [0.14, 2.02], 0.3565	
OR [95%-CI]; p-value	1.94 [0.20, 18.79], 0.5617		0.09 [0.00, 1.86], 0.0564		0.51 [0.12, 2.15], 0.3506	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5198		-0.13 [-0.28, 0.03], 0.1043		-0.05 [-0.16, 0.06], 0.3891	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.2999		0.1413		0.1952	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	5/23 (21.7)	5/48 (10.4)	0/16 (0.0)	9/84 (10.7)	5/39 (12.8)
RR [95%-CI]; p-value	0.51 [0.15, 1.71], 0.2755		3.44 [0.20, 59.59], 0.3963		0.84 [0.30, 2.33], 0.7315	
OR [95%-CI]; p-value	0.45 [0.11, 1.89], 0.2681		3.72 [0.19, 72.04], 0.3541		0.82 [0.25, 2.62], 0.7322	
RD [95%-CI]; p-value	-0.11 [-0.30, 0.09], 0.2912		0.07 [-0.05, 0.19], 0.2262		-0.02 [-0.15, 0.10], 0.7393	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	11/42 (26.2)	3/22 (13.6)	5/37 (13.5)	2/23 (8.7)	16/79 (20.3)	5/45 (11.1)
RR [95%-CI]; p-value	1.92 [0.60, 6.17], 0.2733		1.55 [0.33, 7.36], 0.5784		1.82 [0.72, 4.64], 0.2083	
OR [95%-CI]; p-value	2.25 [0.56, 9.10], 0.2485		1.64 [0.29, 9.25], 0.5719		2.03 [0.69, 5.98], 0.1919	
RD [95%-CI]; p-value	0.13 [-0.07, 0.32], 0.2083		0.05 [-0.11, 0.21], 0.5535		0.09 [-0.04, 0.22], 0.1603	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	5/37 (13.5)	2/17 (11.8)	2/34 (5.9)	5/21 (23.8)	7/71 (9.9)	7/38 (18.4)
RR [95%-CI]; p-value	1.15 [0.25, 5.34], 0.8596		0.25 [0.05, 1.16], 0.0765		0.54 [0.20, 1.41], 0.2069	
OR [95%-CI]; p-value	1.17 [0.20, 6.75], 0.8590		0.20 [0.03, 1.15], 0.0526		0.48 [0.16, 1.50], 0.2030	
RD [95%-CI]; p-value	0.02 [-0.17, 0.21], 0.8558		-0.18 [-0.38, 0.02], 0.0768		-0.09 [-0.23, 0.06], 0.2354	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.6491		0.9444		0.5375	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	2/39 (5.1)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		1.37 [0.07, 28.98], 0.8378		0.93 [0.18, 4.86], 0.9300	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		1.39 [0.06, 32.49], 0.8366		0.93 [0.16, 5.28], 0.9301	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		0.01 [-0.09, 0.11], 0.8241		-0.00 [-0.09, 0.08], 0.9310	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	0/22 (0.0)	2/37 (5.4)	0/23 (0.0)	5/79 (6.3)	0/45 (0.0)
RR [95%-CI]; p-value	3.21 [0.17, 61.40], 0.4379		2.54 [0.12, 53.94], 0.5498		5.76 [0.32, 103.02], 0.2341	
OR [95%-CI]; p-value	3.38 [0.16, 70.70], 0.4057		2.63 [0.11, 60.93], 0.5324		6.08 [0.32, 113.95], 0.1714	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3294		0.03 [-0.06, 0.13], 0.4913		0.05 [-0.01, 0.11], 0.0963	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	3/37 (8.1)	1/17 (5.9)	1/34 (2.9)	0/21 (0.0)	4/71 (5.6)	1/38 (2.6)
RR [95%-CI]; p-value	1.38 [0.15, 12.31], 0.7739		1.26 [0.04, 36.10], 0.8908		2.14 [0.25, 18.48], 0.4889	
OR [95%-CI]; p-value	1.41 [0.14, 14.65], 0.7718		1.27 [0.04, 39.64], 0.8904		2.21 [0.24, 20.50], 0.4753	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7592		0.01 [-0.08, 0.09], 0.8876		0.03 [-0.04, 0.10], 0.4261	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	NA		NA		NA	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	0/48 (0.0)	0/16 (0.0)	0/84 (0.0)	0/39 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	0/79 (0.0)	0/45 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	1/17 (5.9)	0/34 (0.0)	0/21 (0.0)	1/71 (1.4)	1/38 (2.6)
RR [95%-CI]; p-value	0.46 [0.03, 6.92], 0.5740		NA		0.54 [0.03, 8.32], 0.6552	
OR [95%-CI]; p-value	0.44 [0.03, 7.56], 0.5655		NA		0.53 [0.03, 8.69], 0.6502	
RD [95%-CI]; p-value	-0.03 [-0.16, 0.09], 0.6137		NA		-0.01 [-0.07, 0.05], 0.6784	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	NA		NA		NA	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	1/23 (4.3)	0/48 (0.0)	0/16 (0.0)	0/84 (0.0)	1/39 (2.6)
RR [95%-CI]; p-value	0.32 [0.01, 9.02], 0.4998		NA		0.23 [0.01, 6.73], 0.3943	
OR [95%-CI]; p-value	0.31 [0.01, 9.49], 0.4755		NA		0.23 [0.01, 6.89], 0.3523	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.5234		NA		-0.02 [-0.07, 0.03], 0.4592	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	0/79 (0.0)	0/45 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	0/37 (0.0)	0/17 (0.0)	0/34 (0.0)	0/21 (0.0)	0/71 (0.0)	0/38 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.6240		0.2210		0.8275	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	23/36 (63.9)	18/23 (78.3)	27/48 (56.3)	6/16 (37.5)	50/84 (59.5)	24/39 (61.5)
RR [95%-CI]; p-value	0.82 [0.59, 1.13], 0.2234		1.50 [0.76, 2.96], 0.2425		0.97 [0.71, 1.31], 0.8303	
OR [95%-CI]; p-value	0.49 [0.15, 1.63], 0.2423		2.14 [0.67, 6.85], 0.1937		0.92 [0.42, 2.00], 0.8318	
RD [95%-CI]; p-value	-0.14 [-0.37, 0.09], 0.2213		0.19 [-0.09, 0.46], 0.1824		-0.02 [-0.21, 0.17], 0.8312	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	25/42 (59.5)	14/22 (63.6)	15/37 (40.5)	13/23 (56.5)	40/79 (50.6)	27/45 (60.0)
RR [95%-CI]; p-value	0.94 [0.63, 1.40], 0.7449		0.72 [0.42, 1.22], 0.2190		0.84 [0.61, 1.17], 0.3030	
OR [95%-CI]; p-value	0.84 [0.29, 2.44], 0.7488		0.52 [0.18, 1.50], 0.2277		0.68 [0.33, 1.44], 0.3142	
RD [95%-CI]; p-value	-0.04 [-0.29, 0.21], 0.7470		-0.16 [-0.42, 0.10], 0.2230		-0.09 [-0.27, 0.09], 0.3096	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	20/37 (54.1)	13/17 (76.5)	18/34 (52.9)	10/21 (47.6)	38/71 (53.5)	23/38 (60.5)
RR [95%-CI]; p-value	0.71 [0.48, 1.05], 0.0869		1.11 [0.64, 1.93], 0.7054		0.88 [0.63, 1.24], 0.4731	
OR [95%-CI]; p-value	0.36 [0.10, 1.32], 0.1166		1.24 [0.42, 3.68], 0.7013		0.75 [0.34, 1.67], 0.4826	
RD [95%-CI]; p-value	-0.22 [-0.48, 0.03], 0.0883		0.05 [-0.22, 0.32], 0.7009		-0.07 [-0.26, 0.12], 0.4790	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.3342		0.7228		0.4005	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	10/23 (43.5)	13/48 (27.1)	3/16 (18.8)	22/84 (26.2)	13/39 (33.3)
RR [95%-CI]; p-value	0.58 [0.28, 1.20], 0.1389		1.44 [0.47, 4.43], 0.5201		0.79 [0.44, 1.39], 0.4077	
OR [95%-CI]; p-value	0.43 [0.14, 1.32], 0.1385		1.61 [0.39, 6.58], 0.5050		0.71 [0.31, 1.62], 0.4139	
RD [95%-CI]; p-value	-0.18 [-0.43, 0.06], 0.1427		0.08 [-0.15, 0.31], 0.4754		-0.07 [-0.25, 0.10], 0.4245	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	18/42 (42.9)	8/22 (36.4)	11/37 (29.7)	5/23 (21.7)	29/79 (36.7)	13/45 (28.9)
RR [95%-CI]; p-value	1.18 [0.61, 2.27], 0.6224		1.37 [0.54, 3.43], 0.5049		1.27 [0.74, 2.19], 0.3865	
OR [95%-CI]; p-value	1.31 [0.45, 3.80], 0.6154		1.52 [0.45, 5.14], 0.4962		1.43 [0.65, 3.15], 0.3763	
RD [95%-CI]; p-value	0.06 [-0.19, 0.32], 0.6116		0.08 [-0.14, 0.30], 0.4841		0.08 [-0.09, 0.25], 0.3667	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	11/37 (29.7)	7/17 (41.2)	12/34 (35.3)	8/21 (38.1)	23/71 (32.4)	15/38 (39.5)
RR [95%-CI]; p-value	0.72 [0.34, 1.53], 0.3970		0.93 [0.46, 1.88], 0.8331		0.82 [0.49, 1.38], 0.4542	
OR [95%-CI]; p-value	0.60 [0.18, 2.00], 0.4073		0.89 [0.29, 2.74], 0.8338		0.73 [0.32, 1.67], 0.4598	
RD [95%-CI]; p-value	-0.11 [-0.39, 0.16], 0.4170		-0.03 [-0.29, 0.23], 0.8344		-0.07 [-0.26, 0.12], 0.4646	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s6.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.2355		0.4177		0.1185	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	3/84 (3.6)	4/39 (10.3)
RR [95%-CI]; p-value	0.43 [0.08, 2.36], 0.3282		0.33 [0.02, 5.03], 0.4275		0.35 [0.08, 1.48], 0.1533	
OR [95%-CI]; p-value	0.39 [0.06, 2.55], 0.3138		0.32 [0.02, 5.42], 0.4068		0.32 [0.07, 1.52], 0.1364	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.08], 0.3489		-0.04 [-0.17, 0.08], 0.5146		-0.07 [-0.17, 0.04], 0.2040	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	0/22 (0.0)	2/37 (5.4)	1/23 (4.3)	8/79 (10.1)	1/45 (2.2)
RR [95%-CI]; p-value	6.43 [0.38, 109.94], 0.1990		1.24 [0.12, 12.95], 0.8555		4.56 [0.59, 35.27], 0.1463	
OR [95%-CI]; p-value	7.33 [0.39, 137.80], 0.1251		1.26 [0.11, 14.70], 0.8550		4.96 [0.60, 41.00], 0.1028	
RD [95%-CI]; p-value	0.12 [-0.00, 0.24], 0.0528		0.01 [-0.10, 0.12], 0.8515		0.08 [-0.00, 0.16], 0.0506	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	1/17 (5.9)	0/34 (0.0)	3/21 (14.3)	4/71 (5.6)	4/38 (10.5)
RR [95%-CI]; p-value	1.84 [0.22, 15.23], 0.5727		0.10 [0.01, 1.93], 0.1277		0.54 [0.14, 2.02], 0.3565	
OR [95%-CI]; p-value	1.94 [0.20, 18.79], 0.5617		0.09 [0.00, 1.86], 0.0564		0.51 [0.12, 2.15], 0.3506	
RD [95%-CI]; p-value	0.05 [-0.10, 0.20], 0.5198		-0.13 [-0.28, 0.03], 0.1043		-0.05 [-0.16, 0.06], 0.3891	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from lnRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_3_1_m_sf_ttl_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.6787		0.9988		0.9101	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	3/23 (13.0)	4/48 (8.3)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.21 [0.02, 1.93], 0.1686		1.33 [0.16, 11.07], 0.7900		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.19 [0.02, 1.96], 0.1261		1.36 [0.14, 13.18], 0.7880		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.10 [-0.25, 0.05], 0.1732		0.02 [-0.12, 0.16], 0.7738		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	4/22 (18.2)	1/37 (2.7)	0/23 (0.0)	6/79 (7.6)	4/45 (8.9)
RR [95%-CI]; p-value	0.65 [0.20, 2.19], 0.4925		1.27 [0.04, 36.39], 0.8889		0.85 [0.25, 2.87], 0.7990	
OR [95%-CI]; p-value	0.61 [0.15, 2.54], 0.4927		1.28 [0.04, 39.64], 0.8885		0.84 [0.22, 3.16], 0.7992	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.13], 0.5142		0.01 [-0.07, 0.08], 0.8856		-0.01 [-0.11, 0.09], 0.8029	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	2/17 (11.8)	2/34 (5.9)	1/21 (4.8)	4/71 (5.6)	3/38 (7.9)
RR [95%-CI]; p-value	0.46 [0.07, 2.99], 0.4160		1.24 [0.12, 12.80], 0.8594		0.71 [0.17, 3.02], 0.6470	
OR [95%-CI]; p-value	0.43 [0.06, 3.33], 0.4073		1.25 [0.11, 14.70], 0.8589		0.70 [0.15, 3.29], 0.6463	
RD [95%-CI]; p-value	-0.06 [-0.23, 0.11], 0.4624		0.01 [-0.11, 0.13], 0.8555		-0.02 [-0.12, 0.08], 0.6613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.7238		0.8795		0.8709	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	8/23 (34.8)	9/48 (18.8)	1/16 (6.3)	18/84 (21.4)	9/39 (23.1)
RR [95%-CI]; p-value	0.72 [0.32, 1.59], 0.4160		3.00 [0.41, 21.88], 0.2785		0.93 [0.46, 1.88], 0.8366	
OR [95%-CI]; p-value	0.63 [0.20, 1.96], 0.4184		3.46 [0.40, 29.72], 0.2330		0.91 [0.37, 2.26], 0.8372	
RD [95%-CI]; p-value	-0.10 [-0.34, 0.14], 0.4255		0.13 [-0.04, 0.29], 0.1306		-0.02 [-0.18, 0.14], 0.8387	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	6/37 (16.2)	2/23 (8.7)	12/79 (15.2)	6/45 (13.3)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		1.86 [0.41, 8.47], 0.4196		1.14 [0.46, 2.83], 0.7787	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		2.03 [0.37, 11.05], 0.4047		1.16 [0.40, 3.35], 0.7778	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.11, 0.15], 0.7745	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	8/34 (23.5)	3/21 (14.3)	14/71 (19.7)	9/38 (23.7)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		1.65 [0.49, 5.52], 0.4190		0.83 [0.40, 1.74], 0.6269	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		1.85 [0.43, 7.92], 0.4051		0.79 [0.31, 2.04], 0.6287	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		0.09 [-0.11, 0.30], 0.3808		-0.04 [-0.20, 0.12], 0.6352	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1454		0.2566		0.0421	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	7/23 (30.4)	5/48 (10.4)	2/16 (12.5)	8/84 (9.5)	9/39 (23.1)
RR [95%-CI]; p-value	0.27 [0.08, 0.95], 0.0418		0.83 [0.18, 3.88], 0.8164		0.41 [0.17, 0.99], 0.0470	
OR [95%-CI]; p-value	0.21 [0.05, 0.91], 0.0273		0.81 [0.14, 4.67], 0.8171		0.35 [0.12, 0.99], 0.0427	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0378		-0.02 [-0.20, 0.16], 0.8241		-0.14 [-0.28, 0.01], 0.0696	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	3/22 (13.6)	6/37 (16.2)	1/23 (4.3)	14/79 (17.7)	4/45 (8.9)
RR [95%-CI]; p-value	1.40 [0.41, 4.74], 0.5921		3.73 [0.48, 29.03], 0.2087		1.99 [0.70, 5.69], 0.1974	
OR [95%-CI]; p-value	1.49 [0.35, 6.29], 0.5858		4.26 [0.48, 37.91], 0.1638		2.21 [0.68, 7.17], 0.1794	
RD [95%-CI]; p-value	0.05 [-0.13, 0.24], 0.5689		0.12 [-0.03, 0.26], 0.1089		0.09 [-0.03, 0.21], 0.1435	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	5/17 (29.4)	3/34 (8.8)	4/21 (19.0)	7/71 (9.9)	9/38 (23.7)
RR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0972		0.46 [0.11, 1.87], 0.2795		0.42 [0.17, 1.03], 0.0579	
OR [95%-CI]; p-value	0.29 [0.07, 1.27], 0.0885		0.41 [0.08, 2.06], 0.2690		0.35 [0.12, 1.04], 0.0519	
RD [95%-CI]; p-value	-0.19 [-0.42, 0.05], 0.1265		-0.10 [-0.30, 0.09], 0.2994		-0.14 [-0.29, 0.01], 0.0745	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.2532		0.5186		0.9220	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	6/23 (26.1)	10/48 (20.8)	3/16 (18.8)	19/84 (22.6)	9/39 (23.1)
RR [95%-CI]; p-value	0.96 [0.39, 2.34], 0.9254		1.11 [0.35, 3.54], 0.8587		0.98 [0.49, 1.97], 0.9550	
OR [95%-CI]; p-value	0.94 [0.29, 3.13], 0.9255		1.14 [0.27, 4.79], 0.8576		0.97 [0.39, 2.40], 0.9551	
RD [95%-CI]; p-value	-0.01 [-0.24, 0.22], 0.9257		0.02 [-0.20, 0.24], 0.8548		-0.00 [-0.16, 0.16], 0.9552	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	15/42 (35.7)	5/22 (22.7)	8/37 (21.6)	7/23 (30.4)	23/79 (29.1)	12/45 (26.7)
RR [95%-CI]; p-value	1.57 [0.66, 3.75], 0.3090		0.71 [0.30, 1.70], 0.4415		1.09 [0.60, 1.98], 0.7721	
OR [95%-CI]; p-value	1.89 [0.58, 6.15], 0.2870		0.63 [0.19, 2.06], 0.4434		1.13 [0.50, 2.56], 0.7710	
RD [95%-CI]; p-value	0.13 [-0.10, 0.36], 0.2628		-0.09 [-0.32, 0.14], 0.4529		0.02 [-0.14, 0.19], 0.7692	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	6/17 (35.3)	10/34 (29.4)	4/21 (19.0)	17/71 (23.9)	10/38 (26.3)
RR [95%-CI]; p-value	0.54 [0.21, 1.35], 0.1873		1.54 [0.55, 4.30], 0.4057		0.91 [0.46, 1.79], 0.7837	
OR [95%-CI]; p-value	0.43 [0.12, 1.56], 0.1911		1.77 [0.48, 6.60], 0.3913		0.88 [0.36, 2.18], 0.7846	
RD [95%-CI]; p-value	-0.16 [-0.42, 0.10], 0.2168		0.10 [-0.12, 0.33], 0.3715		-0.02 [-0.20, 0.15], 0.7865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2926		0.3399		0.1560	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	4/23 (17.4)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.06, 1.61], 0.1660		0.83 [0.18, 3.88], 0.8164		0.54 [0.19, 1.51], 0.2397	
OR [95%-CI]; p-value	0.28 [0.05, 1.67], 0.1424		0.81 [0.14, 4.67], 0.8171		0.50 [0.16, 1.60], 0.2366	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1775		-0.02 [-0.20, 0.16], 0.8241		-0.07 [-0.20, 0.06], 0.2793	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	1/22 (4.5)	5/37 (13.5)	1/23 (4.3)	10/79 (12.7)	2/45 (4.4)
RR [95%-CI]; p-value	2.62 [0.33, 21.05], 0.3652		3.11 [0.39, 24.95], 0.2860		2.85 [0.65, 12.43], 0.1638	
OR [95%-CI]; p-value	2.84 [0.31, 25.94], 0.3374		3.44 [0.38, 31.48], 0.2499		3.12 [0.65, 14.91], 0.1369	
RD [95%-CI]; p-value	0.07 [-0.06, 0.20], 0.2710		0.09 [-0.05, 0.23], 0.1934		0.08 [-0.01, 0.18], 0.0897	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	5/17 (29.4)	1/34 (2.9)	2/21 (9.5)	8/71 (11.3)	7/38 (18.4)
RR [95%-CI]; p-value	0.64 [0.24, 1.74], 0.3841		0.31 [0.03, 3.20], 0.3246		0.61 [0.24, 1.56], 0.3027	
OR [95%-CI]; p-value	0.56 [0.15, 2.11], 0.3890		0.29 [0.02, 3.39], 0.2963		0.56 [0.19, 1.69], 0.3016	
RD [95%-CI]; p-value	-0.10 [-0.36, 0.15], 0.4120		-0.07 [-0.20, 0.07], 0.3491		-0.07 [-0.22, 0.07], 0.3287	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.1513		0.2896		0.3517	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	9/23 (39.1)	8/48 (16.7)	2/16 (12.5)	12/84 (14.3)	11/39 (28.2)
RR [95%-CI]; p-value	0.28 [0.10, 0.82], 0.0194		1.33 [0.32, 5.64], 0.6959		0.51 [0.25, 1.05], 0.0658	
OR [95%-CI]; p-value	0.19 [0.05, 0.74], 0.0113		1.40 [0.26, 7.40], 0.6910		0.42 [0.17, 1.07], 0.0654	
RD [95%-CI]; p-value	-0.28 [-0.50, -0.06], 0.0144		0.04 [-0.15, 0.23], 0.6727		-0.14 [-0.30, 0.02], 0.0878	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	11/42 (26.2)	7/22 (31.8)	6/37 (16.2)	2/23 (8.7)	17/79 (21.5)	9/45 (20.0)
RR [95%-CI]; p-value	0.82 [0.37, 1.82], 0.6313		1.86 [0.41, 8.47], 0.4196		1.08 [0.52, 2.21], 0.8421	
OR [95%-CI]; p-value	0.76 [0.25, 2.36], 0.6344		2.03 [0.37, 11.05], 0.4047		1.10 [0.44, 2.71], 0.8416	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.18], 0.6398		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.13, 0.16], 0.8405	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	8/37 (21.6)	3/17 (17.6)	7/34 (20.6)	8/21 (38.1)	15/71 (21.1)	11/38 (28.9)
RR [95%-CI]; p-value	1.23 [0.37, 4.05], 0.7393		0.54 [0.23, 1.27], 0.1589		0.73 [0.37, 1.43], 0.3576	
OR [95%-CI]; p-value	1.29 [0.30, 5.61], 0.7363		0.42 [0.13, 1.41], 0.1567		0.66 [0.27, 1.62], 0.3613	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7287		-0.18 [-0.42, 0.07], 0.1669		-0.08 [-0.25, 0.09], 0.3746	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2515		0.2613		0.0816	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	10/36 (27.8)	7/23 (30.4)	12/48 (25.0)	3/16 (18.8)	22/84 (26.2)	10/39 (25.6)
RR [95%-CI]; p-value	0.91 [0.41, 2.06], 0.8255		1.33 [0.43, 4.13], 0.6183		1.02 [0.54, 1.94], 0.9485	
OR [95%-CI]; p-value	0.88 [0.28, 2.77], 0.8260		1.44 [0.35, 5.95], 0.6093		1.03 [0.43, 2.45], 0.9485	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.21], 0.8270		0.06 [-0.16, 0.29], 0.5896		0.01 [-0.16, 0.17], 0.9483	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	4/42 (9.5)	7/22 (31.8)	4/37 (10.8)	7/23 (30.4)	8/79 (10.1)	14/45 (31.1)
RR [95%-CI]; p-value	0.30 [0.10, 0.91], 0.0340		0.36 [0.12, 1.08], 0.0683		0.33 [0.15, 0.72], 0.0052	
OR [95%-CI]; p-value	0.23 [0.06, 0.88], 0.0247		0.28 [0.07, 1.09], 0.0561		0.25 [0.09, 0.66], 0.0033	
RD [95%-CI]; p-value	-0.22 [-0.44, -0.01], 0.0411		-0.20 [-0.41, 0.02], 0.0710		-0.21 [-0.36, -0.06], 0.0064	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	4/34 (11.8)	4/21 (19.0)	10/71 (14.1)	10/38 (26.3)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		0.62 [0.17, 2.21], 0.4588		0.54 [0.24, 1.17], 0.1177	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		0.57 [0.13, 2.56], 0.4567		0.46 [0.17, 1.23], 0.1159	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		-0.07 [-0.27, 0.13], 0.4750		-0.12 [-0.28, 0.04], 0.1382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8116		0.5748		0.5975	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	4/23 (17.4)	5/48 (10.4)	0/16 (0.0)	9/84 (10.7)	4/39 (10.3)
RR [95%-CI]; p-value	0.64 [0.18, 2.31], 0.4938		3.44 [0.20, 59.59], 0.3963		1.04 [0.34, 3.19], 0.9388	
OR [95%-CI]; p-value	0.59 [0.13, 2.65], 0.4920		3.72 [0.19, 72.04], 0.3541		1.05 [0.30, 3.64], 0.9387	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5077		0.07 [-0.05, 0.19], 0.2262		0.00 [-0.11, 0.12], 0.9383	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	6/22 (27.3)	3/37 (8.1)	3/23 (13.0)	8/79 (10.1)	9/45 (20.0)
RR [95%-CI]; p-value	0.44 [0.15, 1.27], 0.1285		0.62 [0.14, 2.82], 0.5381		0.51 [0.21, 1.22], 0.1292	
OR [95%-CI]; p-value	0.36 [0.10, 1.35], 0.1217		0.59 [0.11, 3.20], 0.5355		0.45 [0.16, 1.27], 0.1243	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.06], 0.1521		-0.05 [-0.21, 0.11], 0.5537		-0.10 [-0.23, 0.04], 0.1501	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	5/34 (14.7)	4/21 (19.0)	7/71 (9.9)	5/38 (13.2)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.77 [0.23, 2.56], 0.6719		0.75 [0.25, 2.20], 0.5997	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.73 [0.17, 3.11], 0.6724		0.72 [0.21, 2.45], 0.6000	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.04 [-0.25, 0.16], 0.6793		-0.03 [-0.16, 0.09], 0.6132	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.2959		0.7912		0.4360	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	4/23 (17.4)	1/48 (2.1)	0/16 (0.0)	2/84 (2.4)	4/39 (10.3)
RR [95%-CI]; p-value	0.16 [0.02, 1.34], 0.0911		0.69 [0.02, 19.56], 0.8264		0.23 [0.04, 1.21], 0.0836	
OR [95%-CI]; p-value	0.14 [0.01, 1.30], 0.0493		0.68 [0.02, 21.27], 0.8257		0.21 [0.04, 1.22], 0.0592	
RD [95%-CI]; p-value	-0.15 [-0.31, 0.02], 0.0806		-0.01 [-0.10, 0.08], 0.8402		-0.08 [-0.18, 0.02], 0.1251	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	2/22 (9.1)	3/37 (8.1)	1/23 (4.3)	3/79 (3.8)	3/45 (6.7)
RR [95%-CI]; p-value	0.13 [0.01, 2.75], 0.1897		1.86 [0.21, 16.87], 0.5792		0.57 [0.12, 2.70], 0.4789	
OR [95%-CI]; p-value	0.12 [0.01, 2.76], 0.1185		1.94 [0.19, 19.87], 0.5702		0.55 [0.11, 2.86], 0.4740	
RD [95%-CI]; p-value	-0.08 [-0.20, 0.05], 0.2125		0.04 [-0.08, 0.16], 0.5430		-0.03 [-0.11, 0.06], 0.5042	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	3/37 (8.1)	1/17 (5.9)	1/34 (2.9)	1/21 (4.8)	4/71 (5.6)	2/38 (5.3)
RR [95%-CI]; p-value	1.38 [0.15, 12.31], 0.7739		0.62 [0.04, 9.36], 0.7282		1.07 [0.21, 5.58], 0.9356	
OR [95%-CI]; p-value	1.41 [0.14, 14.65], 0.7718		0.61 [0.04, 10.24], 0.7260		1.07 [0.19, 6.15], 0.9356	
RD [95%-CI]; p-value	0.02 [-0.12, 0.16], 0.7592		-0.02 [-0.13, 0.09], 0.7395		0.00 [-0.09, 0.09], 0.9349	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1068		0.1759		0.1507	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	6/23 (26.1)	8/48 (16.7)	0/16 (0.0)	11/84 (13.1)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.09, 1.15], 0.0814		5.50 [0.33, 90.61], 0.2331		0.85 [0.34, 2.13], 0.7312	
OR [95%-CI]; p-value	0.26 [0.06, 1.16], 0.0643		6.40 [0.35, 118.11], 0.1578		0.83 [0.28, 2.43], 0.7321	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.02], 0.0832		0.14 [0.00, 0.27], 0.0461		-0.02 [-0.16, 0.11], 0.7382	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	1/22 (4.5)	4/37 (10.8)	2/23 (8.7)	12/79 (15.2)	3/45 (6.7)
RR [95%-CI]; p-value	4.19 [0.56, 31.40], 0.1632		1.24 [0.25, 6.25], 0.7917		2.28 [0.68, 7.65], 0.1826	
OR [95%-CI]; p-value	4.94 [0.58, 42.37], 0.1129		1.27 [0.21, 7.57], 0.7906		2.51 [0.67, 9.41], 0.1617	
RD [95%-CI]; p-value	0.15 [-0.00, 0.29], 0.0536		0.02 [-0.13, 0.17], 0.7858		0.09 [-0.02, 0.19], 0.1205	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	3/17 (17.6)	1/34 (2.9)	3/21 (14.3)	5/71 (7.0)	6/38 (15.8)
RR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4872		0.21 [0.02, 1.85], 0.1585		0.45 [0.15, 1.37], 0.1575	
OR [95%-CI]; p-value	0.57 [0.11, 2.86], 0.4873		0.18 [0.02, 1.88], 0.1155		0.40 [0.11, 1.42], 0.1485	
RD [95%-CI]; p-value	-0.07 [-0.28, 0.14], 0.5175		-0.11 [-0.27, 0.05], 0.1648		-0.09 [-0.22, 0.04], 0.1883	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3647		0.8073		0.3635	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	5/23 (21.7)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	7/39 (17.9)
RR [95%-CI]; p-value	0.26 [0.05, 1.21], 0.0853		0.83 [0.18, 3.88], 0.8164		0.46 [0.17, 1.23], 0.1235	
OR [95%-CI]; p-value	0.21 [0.04, 1.20], 0.0608		0.81 [0.14, 4.67], 0.8171		0.42 [0.13, 1.28], 0.1182	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0855		-0.02 [-0.20, 0.16], 0.8241		-0.10 [-0.23, 0.04], 0.1601	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	1/22 (4.5)	3/37 (8.1)	1/23 (4.3)	6/79 (7.6)	2/45 (4.4)
RR [95%-CI]; p-value	1.57 [0.17, 14.23], 0.6877		1.86 [0.21, 16.87], 0.5792		1.71 [0.36, 8.11], 0.5002	
OR [95%-CI]; p-value	1.62 [0.16, 16.51], 0.6835		1.94 [0.19, 19.87], 0.5702		1.77 [0.34, 9.15], 0.4923	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6629		0.04 [-0.08, 0.16], 0.5430		0.03 [-0.05, 0.12], 0.4617	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	2/17 (11.8)	4/34 (11.8)	3/21 (14.3)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.23 [0.02, 2.36], 0.2161		0.82 [0.20, 3.32], 0.7850		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.21 [0.02, 2.48], 0.1769		0.80 [0.16, 3.99], 0.7852		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2724		-0.03 [-0.21, 0.16], 0.7891		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.1.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.9915		0.2242		0.2183	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.85 [0.21, 3.46], 0.8227		0.33 [0.02, 5.03], 0.4275		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.83 [0.17, 4.12], 0.8229		0.32 [0.02, 5.42], 0.4068		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.15], 0.8254		-0.04 [-0.17, 0.08], 0.5146		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	3/37 (8.1)	0/23 (0.0)	9/79 (11.4)	4/45 (8.9)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		3.81 [0.20, 72.73], 0.3739		1.28 [0.42, 3.93], 0.6640	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		4.06 [0.19, 84.88], 0.3315		1.32 [0.38, 4.55], 0.6617	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.06 [-0.05, 0.17], 0.2668		0.03 [-0.08, 0.13], 0.6518	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	2/34 (5.9)	6/21 (28.6)	4/71 (5.6)	7/38 (18.4)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.21 [0.05, 0.93], 0.0396		0.31 [0.10, 0.98], 0.0460	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.16 [0.03, 0.87], 0.0204		0.26 [0.07, 0.97], 0.0347	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.23 [-0.44, -0.02], 0.0332		-0.13 [-0.26, 0.01], 0.0622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_1_m_soc_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.3.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9802		0.8567		0.7960	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	6/23 (26.1)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	6/39 (15.4)
RR [95%-CI]; p-value	0.21 [0.05, 0.97], 0.0450		1.37 [0.07, 28.98], 0.8378		0.31 [0.09, 1.03], 0.0568	
OR [95%-CI]; p-value	0.17 [0.03, 0.91], 0.0247		1.39 [0.06, 32.49], 0.8366		0.28 [0.07, 1.04], 0.0449	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.01], 0.0385		0.01 [-0.09, 0.11], 0.8241		-0.11 [-0.23, 0.02], 0.0880	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	1/22 (4.5)	1/37 (2.7)	0/23 (0.0)	1/79 (1.3)	1/45 (2.2)
RR [95%-CI]; p-value	0.26 [0.01, 7.42], 0.4298		1.27 [0.04, 36.39], 0.8889		0.57 [0.04, 8.89], 0.6881	
OR [95%-CI]; p-value	0.25 [0.01, 7.76], 0.3947		1.28 [0.04, 39.64], 0.8885		0.56 [0.03, 9.24], 0.6844	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.06], 0.4771		0.01 [-0.07, 0.08], 0.8856		-0.01 [-0.06, 0.04], 0.7056	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	5/17 (29.4)	3/34 (8.8)	0/21 (0.0)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.18 [0.04, 0.85], 0.0306		3.79 [0.20, 72.11], 0.3748		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.14 [0.02, 0.80], 0.0147		4.06 [0.19, 85.37], 0.3320		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.24 [-0.47, -0.01], 0.0395		0.06 [-0.05, 0.18], 0.2667		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_3_m_pt_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.3.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5486		0.5916		0.6215	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	2/39 (5.1)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		1.37 [0.07, 28.98], 0.8378		0.93 [0.18, 4.86], 0.9300	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		1.39 [0.06, 32.49], 0.8366		0.93 [0.16, 5.28], 0.9301	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		0.01 [-0.09, 0.11], 0.8241		-0.00 [-0.09, 0.08], 0.9310	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	1/42 (2.4)	3/22 (13.6)	2/37 (5.4)	2/23 (8.7)	3/79 (3.8)	5/45 (11.1)
RR [95%-CI]; p-value	0.17 [0.02, 1.58], 0.1206		0.62 [0.09, 4.11], 0.6219		0.34 [0.09, 1.36], 0.1283	
OR [95%-CI]; p-value	0.15 [0.02, 1.58], 0.0773		0.60 [0.08, 4.58], 0.6194		0.32 [0.07, 1.39], 0.1109	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1431		-0.03 [-0.17, 0.10], 0.6360		-0.07 [-0.17, 0.03], 0.1560	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	3/17 (17.6)	3/34 (8.8)	0/21 (0.0)	4/71 (5.6)	3/38 (7.9)
RR [95%-CI]; p-value	0.15 [0.02, 1.37], 0.0930		3.79 [0.20, 72.11], 0.3748		0.71 [0.17, 3.02], 0.6470	
OR [95%-CI]; p-value	0.13 [0.01, 1.35], 0.0515		4.06 [0.19, 85.37], 0.3320		0.70 [0.15, 3.29], 0.6463	
RD [95%-CI]; p-value	-0.15 [-0.34, 0.04], 0.1204		0.06 [-0.05, 0.18], 0.2667		-0.02 [-0.12, 0.08], 0.6613	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_3_m_pt_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.3.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.7111		0.3669		0.1460	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	0/48 (0.0)	1/16 (6.3)	2/84 (2.4)	3/39 (7.7)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		0.16 [0.01, 4.69], 0.2913		0.31 [0.05, 1.78], 0.1886	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		0.16 [0.00, 4.89], 0.2297		0.29 [0.05, 1.83], 0.1651	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		-0.05 [-0.17, 0.07], 0.4016		-0.05 [-0.14, 0.04], 0.2461	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	4/42 (9.5)	1/22 (4.5)	2/37 (5.4)	0/23 (0.0)	6/79 (7.6)	1/45 (2.2)
RR [95%-CI]; p-value	2.10 [0.25, 17.63], 0.4961		2.54 [0.12, 53.94], 0.5498		3.42 [0.42, 27.50], 0.2480	
OR [95%-CI]; p-value	2.21 [0.23, 21.08], 0.4809		2.63 [0.11, 60.93], 0.5324		3.62 [0.42, 31.04], 0.2126	
RD [95%-CI]; p-value	0.05 [-0.07, 0.17], 0.4326		0.03 [-0.06, 0.13], 0.4913		0.05 [-0.02, 0.13], 0.1468	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	2/34 (5.9)	5/21 (23.8)	4/71 (5.6)	6/38 (15.8)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.25 [0.05, 1.16], 0.0765		0.36 [0.11, 1.19], 0.0929	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.20 [0.03, 1.15], 0.0526		0.32 [0.08, 1.21], 0.0801	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.18 [-0.38, 0.02], 0.0768		-0.10 [-0.23, 0.03], 0.1192	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_3_m_pt_ae10pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.8.1.1.s6.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8565		0.7924		0.8330	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	1/23 (4.3)	1/48 (2.1)	0/16 (0.0)	1/84 (1.2)	1/39 (2.6)
RR [95%-CI]; p-value	0.32 [0.01, 9.02], 0.4998		0.69 [0.02, 19.56], 0.8264		0.46 [0.03, 7.23], 0.5839	
OR [95%-CI]; p-value	0.31 [0.01, 9.49], 0.4755		0.68 [0.02, 21.27], 0.8257		0.46 [0.03, 7.52], 0.5751	
RD [95%-CI]; p-value	-0.03 [-0.12, 0.06], 0.5234		-0.01 [-0.10, 0.08], 0.8402		-0.01 [-0.07, 0.04], 0.6230	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	1/42 (2.4)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	1/79 (1.3)	0/45 (0.0)
RR [95%-CI]; p-value	1.07 [0.04, 30.72], 0.9679		0.63 [0.01, 30.52], 0.8137		1.15 [0.04, 33.67], 0.9346	
OR [95%-CI]; p-value	1.07 [0.03, 33.27], 0.9678		0.62 [0.01, 32.42], 0.8121		1.15 [0.04, 35.08], 0.9345	
RD [95%-CI]; p-value	0.00 [-0.07, 0.08], 0.9675		-0.01 [-0.08, 0.06], 0.8213		0.00 [-0.04, 0.04], 0.9332	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	1/34 (2.9)	3/21 (14.3)	2/71 (2.8)	3/38 (7.9)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		0.21 [0.02, 1.85], 0.1585		0.36 [0.06, 2.04], 0.2471	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		0.18 [0.02, 1.88], 0.1155		0.34 [0.05, 2.12], 0.2272	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		-0.11 [-0.27, 0.05], 0.1648		-0.05 [-0.14, 0.04], 0.2896	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_8_1_1_m_soc_sae5pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.8.1.2.s6.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_8_1_2_m_pt_sae5pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.5.1.1.s6.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_5_1_1_m_soc_aeg35pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.5.1.2.s6.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_5_1_2_m_pt_aeg35pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.7238		0.8795		0.8709	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	8/23 (34.8)	9/48 (18.8)	1/16 (6.3)	18/84 (21.4)	9/39 (23.1)
RR [95%-CI]; p-value	0.72 [0.32, 1.59], 0.4160		3.00 [0.41, 21.88], 0.2785		0.93 [0.46, 1.88], 0.8366	
OR [95%-CI]; p-value	0.63 [0.20, 1.96], 0.4184		3.46 [0.40, 29.72], 0.2330		0.91 [0.37, 2.26], 0.8372	
RD [95%-CI]; p-value	-0.10 [-0.34, 0.14], 0.4255		0.13 [-0.04, 0.29], 0.1306		-0.02 [-0.18, 0.14], 0.8387	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	6/37 (16.2)	2/23 (8.7)	12/79 (15.2)	6/45 (13.3)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		1.86 [0.41, 8.47], 0.4196		1.14 [0.46, 2.83], 0.7787	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		2.03 [0.37, 11.05], 0.4047		1.16 [0.40, 3.35], 0.7778	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.11, 0.15], 0.7745	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	8/34 (23.5)	3/21 (14.3)	14/71 (19.7)	9/38 (23.7)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		1.65 [0.49, 5.52], 0.4190		0.83 [0.40, 1.74], 0.6269	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		1.85 [0.43, 7.92], 0.4051		0.79 [0.31, 2.04], 0.6287	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		0.09 [-0.11, 0.30], 0.3808		-0.04 [-0.20, 0.12], 0.6352	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1454		0.2566		0.0421	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	7/23 (30.4)	5/48 (10.4)	2/16 (12.5)	8/84 (9.5)	9/39 (23.1)
RR [95%-CI]; p-value	0.27 [0.08, 0.95], 0.0418		0.83 [0.18, 3.88], 0.8164		0.41 [0.17, 0.99], 0.0470	
OR [95%-CI]; p-value	0.21 [0.05, 0.91], 0.0273		0.81 [0.14, 4.67], 0.8171		0.35 [0.12, 0.99], 0.0427	
RD [95%-CI]; p-value	-0.22 [-0.43, -0.01], 0.0378		-0.02 [-0.20, 0.16], 0.8241		-0.14 [-0.28, 0.01], 0.0696	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	3/22 (13.6)	6/37 (16.2)	1/23 (4.3)	14/79 (17.7)	4/45 (8.9)
RR [95%-CI]; p-value	1.40 [0.41, 4.74], 0.5921		3.73 [0.48, 29.03], 0.2087		1.99 [0.70, 5.69], 0.1974	
OR [95%-CI]; p-value	1.49 [0.35, 6.29], 0.5858		4.26 [0.48, 37.91], 0.1638		2.21 [0.68, 7.17], 0.1794	
RD [95%-CI]; p-value	0.05 [-0.13, 0.24], 0.5689		0.12 [-0.03, 0.26], 0.1089		0.09 [-0.03, 0.21], 0.1435	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	5/17 (29.4)	3/34 (8.8)	4/21 (19.0)	7/71 (9.9)	9/38 (23.7)
RR [95%-CI]; p-value	0.37 [0.11, 1.20], 0.0972		0.46 [0.11, 1.87], 0.2795		0.42 [0.17, 1.03], 0.0579	
OR [95%-CI]; p-value	0.29 [0.07, 1.27], 0.0885		0.41 [0.08, 2.06], 0.2690		0.35 [0.12, 1.04], 0.0519	
RD [95%-CI]; p-value	-0.19 [-0.42, 0.05], 0.1265		-0.10 [-0.30, 0.09], 0.2994		-0.14 [-0.29, 0.01], 0.0745	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.2532		0.5186		0.9220	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	9/36 (25.0)	6/23 (26.1)	10/48 (20.8)	3/16 (18.8)	19/84 (22.6)	9/39 (23.1)
RR [95%-CI]; p-value	0.96 [0.39, 2.34], 0.9254		1.11 [0.35, 3.54], 0.8587		0.98 [0.49, 1.97], 0.9550	
OR [95%-CI]; p-value	0.94 [0.29, 3.13], 0.9255		1.14 [0.27, 4.79], 0.8576		0.97 [0.39, 2.40], 0.9551	
RD [95%-CI]; p-value	-0.01 [-0.24, 0.22], 0.9257		0.02 [-0.20, 0.24], 0.8548		-0.00 [-0.16, 0.16], 0.9552	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	15/42 (35.7)	5/22 (22.7)	8/37 (21.6)	7/23 (30.4)	23/79 (29.1)	12/45 (26.7)
RR [95%-CI]; p-value	1.57 [0.66, 3.75], 0.3090		0.71 [0.30, 1.70], 0.4415		1.09 [0.60, 1.98], 0.7721	
OR [95%-CI]; p-value	1.89 [0.58, 6.15], 0.2870		0.63 [0.19, 2.06], 0.4434		1.13 [0.50, 2.56], 0.7710	
RD [95%-CI]; p-value	0.13 [-0.10, 0.36], 0.2628		-0.09 [-0.32, 0.14], 0.4529		0.02 [-0.14, 0.19], 0.7692	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	6/17 (35.3)	10/34 (29.4)	4/21 (19.0)	17/71 (23.9)	10/38 (26.3)
RR [95%-CI]; p-value	0.54 [0.21, 1.35], 0.1873		1.54 [0.55, 4.30], 0.4057		0.91 [0.46, 1.79], 0.7837	
OR [95%-CI]; p-value	0.43 [0.12, 1.56], 0.1911		1.77 [0.48, 6.60], 0.3913		0.88 [0.36, 2.18], 0.7846	
RD [95%-CI]; p-value	-0.16 [-0.42, 0.10], 0.2168		0.10 [-0.12, 0.33], 0.3715		-0.02 [-0.20, 0.15], 0.7865	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.5867		0.6743		0.3149	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	2/23 (8.7)	2/48 (4.2)	1/16 (6.3)	4/84 (4.8)	3/39 (7.7)
RR [95%-CI]; p-value	0.64 [0.10, 4.22], 0.6420		0.67 [0.06, 6.87], 0.7334		0.62 [0.15, 2.63], 0.5162	
OR [95%-CI]; p-value	0.62 [0.08, 4.72], 0.6398		0.65 [0.06, 7.71], 0.7328		0.60 [0.13, 2.82], 0.5139	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6540		-0.02 [-0.15, 0.11], 0.7560		-0.03 [-0.12, 0.07], 0.5464	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	3/22 (13.6)	2/37 (5.4)	0/23 (0.0)	7/79 (8.9)	3/45 (6.7)
RR [95%-CI]; p-value	0.87 [0.23, 3.32], 0.8420		2.54 [0.12, 53.94], 0.5498		1.33 [0.36, 4.89], 0.6684	
OR [95%-CI]; p-value	0.86 [0.18, 3.97], 0.8423		2.63 [0.11, 60.93], 0.5324		1.36 [0.33, 5.55], 0.6661	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.16], 0.8451		0.03 [-0.06, 0.13], 0.4913		0.02 [-0.07, 0.12], 0.6546	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	0/17 (0.0)	4/34 (11.8)	1/21 (4.8)	8/71 (11.3)	1/38 (2.6)
RR [95%-CI]; p-value	3.78 [0.21, 67.70], 0.3659		2.47 [0.30, 20.64], 0.4037		4.28 [0.56, 32.97], 0.1626	
OR [95%-CI]; p-value	4.12 [0.21, 82.58], 0.3192		2.67 [0.28, 25.64], 0.3801		4.70 [0.57, 39.07], 0.1185	
RD [95%-CI]; p-value	0.08 [-0.05, 0.21], 0.2193		0.07 [-0.07, 0.21], 0.3321		0.09 [-0.00, 0.18], 0.0584	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.2926		0.3399		0.1560	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	4/23 (17.4)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.06, 1.61], 0.1660		0.83 [0.18, 3.88], 0.8164		0.54 [0.19, 1.51], 0.2397	
OR [95%-CI]; p-value	0.28 [0.05, 1.67], 0.1424		0.81 [0.14, 4.67], 0.8171		0.50 [0.16, 1.60], 0.2366	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1775		-0.02 [-0.20, 0.16], 0.8241		-0.07 [-0.20, 0.06], 0.2793	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	1/22 (4.5)	5/37 (13.5)	1/23 (4.3)	10/79 (12.7)	2/45 (4.4)
RR [95%-CI]; p-value	2.62 [0.33, 21.05], 0.3652		3.11 [0.39, 24.95], 0.2860		2.85 [0.65, 12.43], 0.1638	
OR [95%-CI]; p-value	2.84 [0.31, 25.94], 0.3374		3.44 [0.38, 31.48], 0.2499		3.12 [0.65, 14.91], 0.1369	
RD [95%-CI]; p-value	0.07 [-0.06, 0.20], 0.2710		0.09 [-0.05, 0.23], 0.1934		0.08 [-0.01, 0.18], 0.0897	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	5/17 (29.4)	1/34 (2.9)	2/21 (9.5)	8/71 (11.3)	7/38 (18.4)
RR [95%-CI]; p-value	0.64 [0.24, 1.74], 0.3841		0.31 [0.03, 3.20], 0.3246		0.61 [0.24, 1.56], 0.3027	
OR [95%-CI]; p-value	0.56 [0.15, 2.11], 0.3890		0.29 [0.02, 3.39], 0.2963		0.56 [0.19, 1.69], 0.3016	
RD [95%-CI]; p-value	-0.10 [-0.36, 0.15], 0.4120		-0.07 [-0.20, 0.07], 0.3491		-0.07 [-0.22, 0.07], 0.3287	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.1513		0.2896		0.3517	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	9/23 (39.1)	8/48 (16.7)	2/16 (12.5)	12/84 (14.3)	11/39 (28.2)
RR [95%-CI]; p-value	0.28 [0.10, 0.82], 0.0194		1.33 [0.32, 5.64], 0.6959		0.51 [0.25, 1.05], 0.0658	
OR [95%-CI]; p-value	0.19 [0.05, 0.74], 0.0113		1.40 [0.26, 7.40], 0.6910		0.42 [0.17, 1.07], 0.0654	
RD [95%-CI]; p-value	-0.28 [-0.50, -0.06], 0.0144		0.04 [-0.15, 0.23], 0.6727		-0.14 [-0.30, 0.02], 0.0878	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	11/42 (26.2)	7/22 (31.8)	6/37 (16.2)	2/23 (8.7)	17/79 (21.5)	9/45 (20.0)
RR [95%-CI]; p-value	0.82 [0.37, 1.82], 0.6313		1.86 [0.41, 8.47], 0.4196		1.08 [0.52, 2.21], 0.8421	
OR [95%-CI]; p-value	0.76 [0.25, 2.36], 0.6344		2.03 [0.37, 11.05], 0.4047		1.10 [0.44, 2.71], 0.8416	
RD [95%-CI]; p-value	-0.06 [-0.29, 0.18], 0.6398		0.08 [-0.09, 0.24], 0.3729		0.02 [-0.13, 0.16], 0.8405	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	8/37 (21.6)	3/17 (17.6)	7/34 (20.6)	8/21 (38.1)	15/71 (21.1)	11/38 (28.9)
RR [95%-CI]; p-value	1.23 [0.37, 4.05], 0.7393		0.54 [0.23, 1.27], 0.1589		0.73 [0.37, 1.43], 0.3576	
OR [95%-CI]; p-value	1.29 [0.30, 5.61], 0.7363		0.42 [0.13, 1.41], 0.1567		0.66 [0.27, 1.62], 0.3613	
RD [95%-CI]; p-value	0.04 [-0.18, 0.26], 0.7287		-0.18 [-0.42, 0.07], 0.1669		-0.08 [-0.25, 0.09], 0.3746	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2515		0.2613		0.0816	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	10/36 (27.8)	7/23 (30.4)	12/48 (25.0)	3/16 (18.8)	22/84 (26.2)	10/39 (25.6)
RR [95%-CI]; p-value	0.91 [0.41, 2.06], 0.8255		1.33 [0.43, 4.13], 0.6183		1.02 [0.54, 1.94], 0.9485	
OR [95%-CI]; p-value	0.88 [0.28, 2.77], 0.8260		1.44 [0.35, 5.95], 0.6093		1.03 [0.43, 2.45], 0.9485	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.21], 0.8270		0.06 [-0.16, 0.29], 0.5896		0.01 [-0.16, 0.17], 0.9483	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	4/42 (9.5)	7/22 (31.8)	4/37 (10.8)	7/23 (30.4)	8/79 (10.1)	14/45 (31.1)
RR [95%-CI]; p-value	0.30 [0.10, 0.91], 0.0340		0.36 [0.12, 1.08], 0.0683		0.33 [0.15, 0.72], 0.0052	
OR [95%-CI]; p-value	0.23 [0.06, 0.88], 0.0247		0.28 [0.07, 1.09], 0.0561		0.25 [0.09, 0.66], 0.0033	
RD [95%-CI]; p-value	-0.22 [-0.44, -0.01], 0.0411		-0.20 [-0.41, 0.02], 0.0710		-0.21 [-0.36, -0.06], 0.0064	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	6/37 (16.2)	6/17 (35.3)	4/34 (11.8)	4/21 (19.0)	10/71 (14.1)	10/38 (26.3)
RR [95%-CI]; p-value	0.46 [0.17, 1.22], 0.1180		0.62 [0.17, 2.21], 0.4588		0.54 [0.24, 1.17], 0.1177	
OR [95%-CI]; p-value	0.35 [0.09, 1.33], 0.1173		0.57 [0.13, 2.56], 0.4567		0.46 [0.17, 1.23], 0.1159	
RD [95%-CI]; p-value	-0.19 [-0.45, 0.07], 0.1447		-0.07 [-0.27, 0.13], 0.4750		-0.12 [-0.28, 0.04], 0.1382	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8116		0.5748		0.5975	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	4/23 (17.4)	5/48 (10.4)	0/16 (0.0)	9/84 (10.7)	4/39 (10.3)
RR [95%-CI]; p-value	0.64 [0.18, 2.31], 0.4938		3.44 [0.20, 59.59], 0.3963		1.04 [0.34, 3.19], 0.9388	
OR [95%-CI]; p-value	0.59 [0.13, 2.65], 0.4920		3.72 [0.19, 72.04], 0.3541		1.05 [0.30, 3.64], 0.9387	
RD [95%-CI]; p-value	-0.06 [-0.25, 0.12], 0.5077		0.07 [-0.05, 0.19], 0.2262		0.00 [-0.11, 0.12], 0.9383	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	5/42 (11.9)	6/22 (27.3)	3/37 (8.1)	3/23 (13.0)	8/79 (10.1)	9/45 (20.0)
RR [95%-CI]; p-value	0.44 [0.15, 1.27], 0.1285		0.62 [0.14, 2.82], 0.5381		0.51 [0.21, 1.22], 0.1292	
OR [95%-CI]; p-value	0.36 [0.10, 1.35], 0.1217		0.59 [0.11, 3.20], 0.5355		0.45 [0.16, 1.27], 0.1243	
RD [95%-CI]; p-value	-0.15 [-0.36, 0.06], 0.1521		-0.05 [-0.21, 0.11], 0.5537		-0.10 [-0.23, 0.04], 0.1501	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	5/34 (14.7)	4/21 (19.0)	7/71 (9.9)	5/38 (13.2)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.77 [0.23, 2.56], 0.6719		0.75 [0.25, 2.20], 0.5997	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.73 [0.17, 3.11], 0.6724		0.72 [0.21, 2.45], 0.6000	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.04 [-0.25, 0.16], 0.6793		-0.03 [-0.16, 0.09], 0.6132	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1068		0.1759		0.1507	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	3/36 (8.3)	6/23 (26.1)	8/48 (16.7)	0/16 (0.0)	11/84 (13.1)	6/39 (15.4)
RR [95%-CI]; p-value	0.32 [0.09, 1.15], 0.0814		5.50 [0.33, 90.61], 0.2331		0.85 [0.34, 2.13], 0.7312	
OR [95%-CI]; p-value	0.26 [0.06, 1.16], 0.0643		6.40 [0.35, 118.11], 0.1578		0.83 [0.28, 2.43], 0.7321	
RD [95%-CI]; p-value	-0.18 [-0.38, 0.02], 0.0832		0.14 [0.00, 0.27], 0.0461		-0.02 [-0.16, 0.11], 0.7382	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	8/42 (19.0)	1/22 (4.5)	4/37 (10.8)	2/23 (8.7)	12/79 (15.2)	3/45 (6.7)
RR [95%-CI]; p-value	4.19 [0.56, 31.40], 0.1632		1.24 [0.25, 6.25], 0.7917		2.28 [0.68, 7.65], 0.1826	
OR [95%-CI]; p-value	4.94 [0.58, 42.37], 0.1129		1.27 [0.21, 7.57], 0.7906		2.51 [0.67, 9.41], 0.1617	
RD [95%-CI]; p-value	0.15 [-0.00, 0.29], 0.0536		0.02 [-0.13, 0.17], 0.7858		0.09 [-0.02, 0.19], 0.1205	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	4/37 (10.8)	3/17 (17.6)	1/34 (2.9)	3/21 (14.3)	5/71 (7.0)	6/38 (15.8)
RR [95%-CI]; p-value	0.61 [0.15, 2.44], 0.4872		0.21 [0.02, 1.85], 0.1585		0.45 [0.15, 1.37], 0.1575	
OR [95%-CI]; p-value	0.57 [0.11, 2.86], 0.4873		0.18 [0.02, 1.88], 0.1155		0.40 [0.11, 1.42], 0.1485	
RD [95%-CI]; p-value	-0.07 [-0.28, 0.14], 0.5175		-0.11 [-0.27, 0.05], 0.1648		-0.09 [-0.22, 0.04], 0.1883	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.3647		0.8073		0.3635	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	5/23 (21.7)	5/48 (10.4)	2/16 (12.5)	7/84 (8.3)	7/39 (17.9)
RR [95%-CI]; p-value	0.26 [0.05, 1.21], 0.0853		0.83 [0.18, 3.88], 0.8164		0.46 [0.17, 1.23], 0.1235	
OR [95%-CI]; p-value	0.21 [0.04, 1.20], 0.0608		0.81 [0.14, 4.67], 0.8171		0.42 [0.13, 1.28], 0.1182	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.02], 0.0855		-0.02 [-0.20, 0.16], 0.8241		-0.10 [-0.23, 0.04], 0.1601	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	1/22 (4.5)	3/37 (8.1)	1/23 (4.3)	6/79 (7.6)	2/45 (4.4)
RR [95%-CI]; p-value	1.57 [0.17, 14.23], 0.6877		1.86 [0.21, 16.87], 0.5792		1.71 [0.36, 8.11], 0.5002	
OR [95%-CI]; p-value	1.62 [0.16, 16.51], 0.6835		1.94 [0.19, 19.87], 0.5702		1.77 [0.34, 9.15], 0.4923	
RD [95%-CI]; p-value	0.03 [-0.09, 0.14], 0.6629		0.04 [-0.08, 0.16], 0.5430		0.03 [-0.05, 0.12], 0.4617	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	2/17 (11.8)	4/34 (11.8)	3/21 (14.3)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.23 [0.02, 2.36], 0.2161		0.82 [0.20, 3.32], 0.7850		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.21 [0.02, 2.48], 0.1769		0.80 [0.16, 3.99], 0.7852		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.09 [-0.25, 0.07], 0.2724		-0.03 [-0.21, 0.16], 0.7891		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.2.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.9915		0.2242		0.2183	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	4/36 (11.1)	3/23 (13.0)	1/48 (2.1)	1/16 (6.3)	5/84 (6.0)	4/39 (10.3)
RR [95%-CI]; p-value	0.85 [0.21, 3.46], 0.8227		0.33 [0.02, 5.03], 0.4275		0.58 [0.16, 2.04], 0.3969	
OR [95%-CI]; p-value	0.83 [0.17, 4.12], 0.8229		0.32 [0.02, 5.42], 0.4068		0.55 [0.14, 2.19], 0.3937	
RD [95%-CI]; p-value	-0.02 [-0.19, 0.15], 0.8254		-0.04 [-0.17, 0.08], 0.5146		-0.04 [-0.15, 0.06], 0.4340	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	6/42 (14.3)	4/22 (18.2)	3/37 (8.1)	0/23 (0.0)	9/79 (11.4)	4/45 (8.9)
RR [95%-CI]; p-value	0.79 [0.25, 2.49], 0.6824		3.81 [0.20, 72.73], 0.3739		1.28 [0.42, 3.93], 0.6640	
OR [95%-CI]; p-value	0.75 [0.19, 3.00], 0.6835		4.06 [0.19, 84.88], 0.3315		1.32 [0.38, 4.55], 0.6617	
RD [95%-CI]; p-value	-0.04 [-0.23, 0.15], 0.6921		0.06 [-0.05, 0.17], 0.2668		0.03 [-0.08, 0.13], 0.6518	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	1/17 (5.9)	2/34 (5.9)	6/21 (28.6)	4/71 (5.6)	7/38 (18.4)
RR [95%-CI]; p-value	0.92 [0.09, 9.45], 0.9433		0.21 [0.05, 0.93], 0.0396		0.31 [0.10, 0.98], 0.0460	
OR [95%-CI]; p-value	0.91 [0.08, 10.83], 0.9433		0.16 [0.03, 0.87], 0.0204		0.26 [0.07, 0.97], 0.0347	
RD [95%-CI]; p-value	-0.00 [-0.14, 0.13], 0.9442		-0.23 [-0.44, -0.02], 0.0332		-0.13 [-0.26, 0.01], 0.0622	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_2_m_soc_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.4.s6.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9802		0.8567		0.7960	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	2/36 (5.6)	6/23 (26.1)	2/48 (4.2)	0/16 (0.0)	4/84 (4.8)	6/39 (15.4)
RR [95%-CI]; p-value	0.21 [0.05, 0.97], 0.0450		1.37 [0.07, 28.98], 0.8378		0.31 [0.09, 1.03], 0.0568	
OR [95%-CI]; p-value	0.17 [0.03, 0.91], 0.0247		1.39 [0.06, 32.49], 0.8366		0.28 [0.07, 1.04], 0.0449	
RD [95%-CI]; p-value	-0.21 [-0.40, -0.01], 0.0385		0.01 [-0.09, 0.11], 0.8241		-0.11 [-0.23, 0.02], 0.0880	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	1/22 (4.5)	1/37 (2.7)	0/23 (0.0)	1/79 (1.3)	1/45 (2.2)
RR [95%-CI]; p-value	0.26 [0.01, 7.42], 0.4298		1.27 [0.04, 36.39], 0.8889		0.57 [0.04, 8.89], 0.6881	
OR [95%-CI]; p-value	0.25 [0.01, 7.76], 0.3947		1.28 [0.04, 39.64], 0.8885		0.56 [0.03, 9.24], 0.6844	
RD [95%-CI]; p-value	-0.03 [-0.13, 0.06], 0.4771		0.01 [-0.07, 0.08], 0.8856		-0.01 [-0.06, 0.04], 0.7056	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	5/17 (29.4)	3/34 (8.8)	0/21 (0.0)	5/71 (7.0)	5/38 (13.2)
RR [95%-CI]; p-value	0.18 [0.04, 0.85], 0.0306		3.79 [0.20, 72.11], 0.3748		0.54 [0.17, 1.73], 0.2972	
OR [95%-CI]; p-value	0.14 [0.02, 0.80], 0.0147		4.06 [0.19, 85.37], 0.3320		0.50 [0.14, 1.85], 0.2919	
RD [95%-CI]; p-value	-0.24 [-0.47, -0.01], 0.0395		0.06 [-0.05, 0.18], 0.2667		-0.06 [-0.18, 0.06], 0.3292	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_4_m_pt_ae1pct_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.2234		0.9985		0.3397	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	2/23 (8.7)	2/48 (4.2)	1/16 (6.3)	3/84 (3.6)	3/39 (7.7)
RR [95%-CI]; p-value	0.32 [0.03, 3.33], 0.3397		0.67 [0.06, 6.87], 0.7334		0.46 [0.10, 2.20], 0.3334	
OR [95%-CI]; p-value	0.30 [0.03, 3.51], 0.3129		0.65 [0.06, 7.71], 0.7328		0.44 [0.09, 2.31], 0.3235	
RD [95%-CI]; p-value	-0.06 [-0.19, 0.07], 0.3613		-0.02 [-0.15, 0.11], 0.7560		-0.04 [-0.13, 0.05], 0.3829	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	2/42 (4.8)	0/22 (0.0)	1/37 (2.7)	1/23 (4.3)	3/79 (3.8)	1/45 (2.2)
RR [95%-CI]; p-value	2.14 [0.10, 45.54], 0.6250		0.62 [0.04, 9.46], 0.7322		1.71 [0.18, 15.95], 0.6382	
OR [95%-CI]; p-value	2.20 [0.09, 50.95], 0.6145		0.61 [0.04, 10.27], 0.7300		1.74 [0.18, 17.21], 0.6331	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5744		-0.02 [-0.11, 0.08], 0.7431		0.02 [-0.04, 0.08], 0.6084	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	8/37 (21.6)	0/17 (0.0)	3/34 (8.8)	3/21 (14.3)	11/71 (15.5)	3/38 (7.9)
RR [95%-CI]; p-value	7.57 [0.46, 124.44], 0.1566		0.62 [0.14, 2.78], 0.5303		1.96 [0.58, 6.61], 0.2765	
OR [95%-CI]; p-value	9.38 [0.51, 173.76], 0.0746		0.58 [0.11, 3.19], 0.5279		2.14 [0.56, 8.19], 0.2585	
RD [95%-CI]; p-value	0.19 [0.03, 0.34], 0.0169		-0.05 [-0.23, 0.12], 0.5463		0.08 [-0.04, 0.20], 0.2151	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	NA		NA		NA	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	0/48 (0.0)	0/16 (0.0)	0/84 (0.0)	0/39 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	0/37 (0.0)	0/23 (0.0)	0/79 (0.0)	0/45 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	0/34 (0.0)	0/21 (0.0)	1/71 (1.4)	0/38 (0.0)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		NA		1.08 [0.04, 31.60], 0.9624	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		NA		1.09 [0.04, 33.11], 0.9624	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		NA		0.00 [-0.04, 0.05], 0.9619	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.2505		0.9985		0.3831	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	2/23 (8.7)	2/48 (4.2)	1/16 (6.3)	3/84 (3.6)	3/39 (7.7)
RR [95%-CI]; p-value	0.32 [0.03, 3.33], 0.3397		0.67 [0.06, 6.87], 0.7334		0.46 [0.10, 2.20], 0.3334	
OR [95%-CI]; p-value	0.30 [0.03, 3.51], 0.3129		0.65 [0.06, 7.71], 0.7328		0.44 [0.09, 2.31], 0.3235	
RD [95%-CI]; p-value	-0.06 [-0.19, 0.07], 0.3613		-0.02 [-0.15, 0.11], 0.7560		-0.04 [-0.13, 0.05], 0.3829	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	2/42 (4.8)	0/22 (0.0)	1/37 (2.7)	1/23 (4.3)	3/79 (3.8)	1/45 (2.2)
RR [95%-CI]; p-value	2.14 [0.10, 45.54], 0.6250		0.62 [0.04, 9.46], 0.7322		1.71 [0.18, 15.95], 0.6382	
OR [95%-CI]; p-value	2.20 [0.09, 50.95], 0.6145		0.61 [0.04, 10.27], 0.7300		1.74 [0.18, 17.21], 0.6331	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5744		-0.02 [-0.11, 0.08], 0.7431		0.02 [-0.04, 0.08], 0.6084	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	0/17 (0.0)	3/34 (8.8)	3/21 (14.3)	10/71 (14.1)	3/38 (7.9)
RR [95%-CI]; p-value	6.62 [0.40, 110.22], 0.1877		0.62 [0.14, 2.78], 0.5303		1.78 [0.52, 6.10], 0.3558	
OR [95%-CI]; p-value	7.93 [0.42, 148.59], 0.1080		0.58 [0.11, 3.19], 0.5279		1.91 [0.49, 7.42], 0.3420	
RD [95%-CI]; p-value	0.16 [0.01, 0.31], 0.0339		-0.05 [-0.23, 0.12], 0.5463		0.06 [-0.06, 0.18], 0.3034	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.8095		NA		0.5904	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	1/36 (2.8)	1/23 (4.3)	0/48 (0.0)	0/16 (0.0)	1/84 (1.2)	1/39 (2.6)
RR [95%-CI]; p-value	0.64 [0.04, 9.72], 0.7470		NA		0.46 [0.03, 7.23], 0.5839	
OR [95%-CI]; p-value	0.63 [0.04, 10.57], 0.7452		NA		0.46 [0.03, 7.52], 0.5751	
RD [95%-CI]; p-value	-0.02 [-0.11, 0.08], 0.7563		NA		-0.01 [-0.07, 0.04], 0.6230	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	2/42 (4.8)	0/22 (0.0)	1/37 (2.7)	0/23 (0.0)	3/79 (3.8)	0/45 (0.0)
RR [95%-CI]; p-value	2.14 [0.10, 45.54], 0.6250		1.27 [0.04, 36.39], 0.8889		3.46 [0.18, 67.47], 0.4134	
OR [95%-CI]; p-value	2.20 [0.09, 50.95], 0.6145		1.28 [0.04, 39.64], 0.8885		3.55 [0.17, 72.54], 0.3804	
RD [95%-CI]; p-value	0.03 [-0.06, 0.11], 0.5744		0.01 [-0.07, 0.08], 0.8856		0.03 [-0.02, 0.08], 0.3082	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	0/17 (0.0)	0/34 (0.0)	0/21 (0.0)	2/71 (2.8)	0/38 (0.0)
RR [95%-CI]; p-value	1.89 [0.09, 39.80], 0.6817		NA		2.17 [0.10, 46.91], 0.6215	
OR [95%-CI]; p-value	1.94 [0.08, 45.46], 0.6746		NA		2.20 [0.10, 50.10], 0.6116	
RD [95%-CI]; p-value	0.03 [-0.08, 0.13], 0.6400		NA		0.02 [-0.04, 0.07], 0.5711	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.1280		0.4295		0.0679	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	4/23 (17.4)	3/48 (6.3)	1/16 (6.3)	3/84 (3.6)	5/39 (12.8)
RR [95%-CI]; p-value	0.08 [0.00, 1.42], 0.0852		1.00 [0.11, 8.95], 1.0000		0.28 [0.07, 1.11], 0.0695	
OR [95%-CI]; p-value	0.07 [0.00, 1.31], 0.0228		1.00 [0.10, 10.35], 1.0000		0.25 [0.06, 1.11], 0.0529	
RD [95%-CI]; p-value	-0.16 [-0.32, -0.00], 0.0489		0.00 [-0.14, 0.14], 1.0000		-0.09 [-0.20, 0.02], 0.1061	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	7/42 (16.7)	2/22 (9.1)	4/37 (10.8)	1/23 (4.3)	11/79 (13.9)	3/45 (6.7)
RR [95%-CI]; p-value	1.83 [0.42, 8.09], 0.4235		2.49 [0.30, 20.89], 0.4016		2.09 [0.61, 7.10], 0.2379	
OR [95%-CI]; p-value	2.00 [0.38, 10.57], 0.4076		2.67 [0.28, 25.47], 0.3785		2.26 [0.60, 8.59], 0.2195	
RD [95%-CI]; p-value	0.08 [-0.09, 0.24], 0.3674		0.06 [-0.07, 0.19], 0.3307		0.07 [-0.03, 0.18], 0.1778	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	3/37 (8.1)	3/17 (17.6)	2/34 (5.9)	3/21 (14.3)	5/71 (7.0)	6/38 (15.8)
RR [95%-CI]; p-value	0.46 [0.10, 2.05], 0.3075		0.41 [0.07, 2.26], 0.3076		0.45 [0.15, 1.37], 0.1575	
OR [95%-CI]; p-value	0.41 [0.07, 2.29], 0.3002		0.38 [0.06, 2.46], 0.2922		0.40 [0.11, 1.42], 0.1485	
RD [95%-CI]; p-value	-0.10 [-0.30, 0.11], 0.3533		-0.08 [-0.25, 0.09], 0.3306		-0.09 [-0.22, 0.04], 0.1883	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	NA		0.8390		0.9345	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	1/48 (2.1)	0/16 (0.0)	1/84 (1.2)	0/39 (0.0)
RR [95%-CI]; p-value	NA		0.69 [0.02, 19.56], 0.8264		0.94 [0.03, 27.45], 0.9716	
OR [95%-CI]; p-value	NA		0.68 [0.02, 21.27], 0.8257		0.94 [0.03, 28.61], 0.9716	
RD [95%-CI]; p-value	NA		-0.01 [-0.10, 0.08], 0.8402		-0.00 [-0.04, 0.04], 0.9719	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	0/42 (0.0)	0/22 (0.0)	1/37 (2.7)	0/23 (0.0)	1/79 (1.3)	0/45 (0.0)
RR [95%-CI]; p-value	NA		1.27 [0.04, 36.39], 0.8889		1.15 [0.04, 33.67], 0.9346	
OR [95%-CI]; p-value	NA		1.28 [0.04, 39.64], 0.8885		1.15 [0.04, 35.08], 0.9345	
RD [95%-CI]; p-value	NA		0.01 [-0.07, 0.08], 0.8856		0.00 [-0.04, 0.04], 0.9332	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	0/34 (0.0)	1/21 (4.8)	1/71 (1.4)	1/38 (2.6)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		0.30 [0.01, 8.68], 0.4866		0.54 [0.03, 8.32], 0.6552	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		0.29 [0.01, 9.17], 0.4605		0.53 [0.03, 8.69], 0.6502	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		-0.03 [-0.13, 0.07], 0.5138		-0.01 [-0.07, 0.05], 0.6784	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.0969		0.4282		0.0336	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	4/23 (17.4)	2/48 (4.2)	1/16 (6.3)	2/84 (2.4)	5/39 (12.8)
RR [95%-CI]; p-value	0.08 [0.00, 1.42], 0.0852		0.67 [0.06, 6.87], 0.7334		0.19 [0.04, 0.92], 0.0386	
OR [95%-CI]; p-value	0.07 [0.00, 1.31], 0.0228		0.65 [0.06, 7.71], 0.7328		0.17 [0.03, 0.90], 0.0200	
RD [95%-CI]; p-value	-0.16 [-0.32, -0.00], 0.0489		-0.02 [-0.15, 0.11], 0.7560		-0.10 [-0.21, 0.01], 0.0626	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	7/42 (16.7)	2/22 (9.1)	4/37 (10.8)	1/23 (4.3)	11/79 (13.9)	3/45 (6.7)
RR [95%-CI]; p-value	1.83 [0.42, 8.09], 0.4235		2.49 [0.30, 20.89], 0.4016		2.09 [0.61, 7.10], 0.2379	
OR [95%-CI]; p-value	2.00 [0.38, 10.57], 0.4076		2.67 [0.28, 25.47], 0.3785		2.26 [0.60, 8.59], 0.2195	
RD [95%-CI]; p-value	0.08 [-0.09, 0.24], 0.3674		0.06 [-0.07, 0.19], 0.3307		0.07 [-0.03, 0.18], 0.1778	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	2/37 (5.4)	3/17 (17.6)	2/34 (5.9)	3/21 (14.3)	4/71 (5.6)	6/38 (15.8)
RR [95%-CI]; p-value	0.31 [0.06, 1.67], 0.1712		0.41 [0.07, 2.26], 0.3076		0.36 [0.11, 1.19], 0.0929	
OR [95%-CI]; p-value	0.27 [0.04, 1.77], 0.1495		0.38 [0.06, 2.46], 0.2922		0.32 [0.08, 1.21], 0.0801	
RD [95%-CI]; p-value	-0.12 [-0.32, 0.07], 0.2193		-0.08 [-0.25, 0.09], 0.3306		-0.10 [-0.23, 0.03], 0.1192	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.7.s6.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.7749		0.7744		0.5691	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	0/36 (0.0)	0/23 (0.0)	2/48 (4.2)	0/16 (0.0)	2/84 (2.4)	0/39 (0.0)
RR [95%-CI]; p-value	NA		1.37 [0.07, 28.98], 0.8378		1.88 [0.09, 40.76], 0.6873	
OR [95%-CI]; p-value	NA		1.39 [0.06, 32.49], 0.8366		1.90 [0.08, 43.18], 0.6815	
RD [95%-CI]; p-value	NA		0.01 [-0.09, 0.11], 0.8241		0.01 [-0.04, 0.06], 0.6470	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	0/22 (0.0)	1/37 (2.7)	0/23 (0.0)	4/79 (5.1)	0/45 (0.0)
RR [95%-CI]; p-value	3.21 [0.17, 61.40], 0.4379		1.27 [0.04, 36.39], 0.8889		4.61 [0.25, 85.19], 0.3047	
OR [95%-CI]; p-value	3.38 [0.16, 70.70], 0.4057		1.28 [0.04, 39.64], 0.8885		4.80 [0.25, 92.92], 0.2538	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3294		0.01 [-0.07, 0.08], 0.8856		0.04 [-0.02, 0.10], 0.1732	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	1/37 (2.7)	0/17 (0.0)	0/34 (0.0)	1/21 (4.8)	1/71 (1.4)	1/38 (2.6)
RR [95%-CI]; p-value	0.95 [0.03, 26.88], 0.9740		0.30 [0.01, 8.68], 0.4866		0.54 [0.03, 8.32], 0.6552	
OR [95%-CI]; p-value	0.94 [0.03, 29.55], 0.9740		0.29 [0.01, 9.17], 0.4605		0.53 [0.03, 8.69], 0.6502	
RD [95%-CI]; p-value	-0.00 [-0.10, 0.09], 0.9743		-0.03 [-0.13, 0.07], 0.5138		-0.01 [-0.07, 0.05], 0.6784	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity. Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_7_m_pt_smq_ttlpth_pp.sas using SAS 9.4

Table 12.4.4.1.6.s6.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: Tertiles of Baseline PTH

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.9209		0.9261		0.8527	
1st Tertile:	N1=36	N1=23	N1=48	N1=16	N1=84	N1=39
n/N1 (%)	6/36 (16.7)	7/23 (30.4)	10/48 (20.8)	2/16 (12.5)	16/84 (19.0)	9/39 (23.1)
RR [95%-CI]; p-value	0.55 [0.21, 1.43], 0.2173		1.67 [0.41, 6.82], 0.4773		0.83 [0.40, 1.70], 0.6029	
OR [95%-CI]; p-value	0.46 [0.13, 1.59], 0.2133		1.84 [0.36, 9.47], 0.4595		0.78 [0.31, 1.97], 0.6053	
RD [95%-CI]; p-value	-0.14 [-0.36, 0.09], 0.2284		0.08 [-0.12, 0.28], 0.4109		-0.04 [-0.20, 0.12], 0.6141	
2nd Tertile:	N2=42	N2=22	N2=37	N2=23	N2=79	N2=45
n/N2 (%)	3/42 (7.1)	4/22 (18.2)	4/37 (10.8)	2/23 (8.7)	7/79 (8.9)	6/45 (13.3)
RR [95%-CI]; p-value	0.39 [0.10, 1.60], 0.1925		1.24 [0.25, 6.25], 0.7917		0.66 [0.24, 1.86], 0.4355	
OR [95%-CI]; p-value	0.35 [0.07, 1.71], 0.1790		1.27 [0.21, 7.57], 0.7906		0.63 [0.20, 2.01], 0.4344	
RD [95%-CI]; p-value	-0.11 [-0.29, 0.07], 0.2268		0.02 [-0.13, 0.17], 0.7858		-0.04 [-0.16, 0.07], 0.4554	
3rd Tertile:	N3=37	N3=17	N3=34	N3=21	N3=71	N3=38
n/N3 (%)	7/37 (18.9)	6/17 (35.3)	9/34 (26.5)	3/21 (14.3)	16/71 (22.5)	9/38 (23.7)
RR [95%-CI]; p-value	0.54 [0.21, 1.35], 0.1873		1.85 [0.56, 6.08], 0.3089		0.95 [0.47, 1.95], 0.8916	
OR [95%-CI]; p-value	0.43 [0.12, 1.56], 0.1911		2.16 [0.51, 9.12], 0.2878		0.94 [0.37, 2.38], 0.8918	
RD [95%-CI]; p-value	-0.16 [-0.42, 0.10], 0.2168		0.12 [-0.09, 0.33], 0.2570		-0.01 [-0.18, 0.15], 0.8924	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
PTH: Parathyroid Hormone; 1st Tertile: Baseline PTH< 113.7 pg/mL; 2nd Tertile: 113.7<=Baseline PTH<153.7 pg/mL; 3rd Tertile: Baseline PTH>=153.7 pg/mL.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s6_ttlpth_pp/T12_4_4_1_6_m_pt_adr_ttlpth_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.2423		0.1208		0.0071	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	8/13 (61.5)	5/5 (100.0)	12/27 (44.4)	3/4 (75.0)	20/40 (50.0)	8/9 (88.9)
RR [95%-CI]; p-value	0.68 [0.41, 1.12], 0.1296		0.59 [0.29, 1.20], 0.1461		0.56 [0.38, 0.83], 0.0035	
OR [95%-CI]; p-value	0.16 [0.01, 3.60], 0.2065		0.27 [0.02, 2.90], 0.2538		0.13 [0.01, 1.09], 0.0332	
RD [95%-CI]; p-value	-0.29 [-0.65, 0.06], 0.1072		-0.31 [-0.77, 0.16], 0.1967		-0.39 [-0.65, -0.13], 0.0030	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	75/102 (73.5)	45/57 (78.9)	60/92 (65.2)	34/56 (60.7)	135/194 (69.6)	79/113 (69.9)
RR [95%-CI]; p-value	0.93 [0.78, 1.11], 0.4326		1.07 [0.83, 1.39], 0.5870		1.00 [0.85, 1.16], 0.9524	
OR [95%-CI]; p-value	0.74 [0.34, 1.61], 0.4464		1.21 [0.61, 2.41], 0.5810		0.98 [0.59, 1.63], 0.9525	
RD [95%-CI]; p-value	-0.05 [-0.19, 0.08], 0.4354		0.05 [-0.12, 0.21], 0.5829		-0.00 [-0.11, 0.10], 0.9525	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.7694		0.3351		0.8970	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	2/40 (5.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		0.67 [0.04, 12.53], 0.7865		0.95 [0.05, 19.41], 0.9734	
OR [95%-CI]; p-value	NA		0.64 [0.02, 16.90], 0.7879		0.95 [0.04, 22.85], 0.9734	
RD [95%-CI]; p-value	NA		-0.04 [-0.34, 0.27], 0.8129		-0.00 [-0.16, 0.15], 0.9738	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	13/102 (12.7)	10/57 (17.5)	11/92 (12.0)	2/56 (3.6)	24/194 (12.4)	12/113 (10.6)
RR [95%-CI]; p-value	0.73 [0.34, 1.55], 0.4087		3.35 [0.77, 14.55], 0.1071		1.16 [0.61, 2.24], 0.6468	
OR [95%-CI]; p-value	0.69 [0.28, 1.68], 0.4094		3.67 [0.78, 17.20], 0.0805		1.19 [0.57, 2.48], 0.6455	
RD [95%-CI]; p-value	-0.05 [-0.17, 0.07], 0.4256		0.08 [0.00, 0.17], 0.0456		0.02 [-0.06, 0.09], 0.6395	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.0314		0.6968		0.0518	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		NA		0.06 [0.00, 1.13], 0.0601	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		NA		0.04 [0.00, 1.07], 0.0093	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		NA		-0.21 [-0.48, 0.06], 0.1329	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	12/102 (11.8)	2/57 (3.5)	3/92 (3.3)	5/56 (8.9)	15/194 (7.7)	7/113 (6.2)
RR [95%-CI]; p-value	3.35 [0.78, 14.46], 0.1047		0.37 [0.09, 1.47], 0.1562		1.25 [0.52, 2.97], 0.6161	
OR [95%-CI]; p-value	3.67 [0.79, 17.00], 0.0781		0.34 [0.08, 1.50], 0.1392		1.27 [0.50, 3.21], 0.6145	
RD [95%-CI]; p-value	0.08 [0.00, 0.16], 0.0397		-0.06 [-0.14, 0.03], 0.1810		0.02 [-0.04, 0.07], 0.6047	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.0993		0.5270		0.0650	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	2/5 (40.0)	3/27 (11.1)	1/4 (25.0)	4/40 (10.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.19 [0.02, 1.68], 0.1360		0.44 [0.06, 3.30], 0.4279		0.30 [0.08, 1.11], 0.0718	
OR [95%-CI]; p-value	0.13 [0.01, 1.89], 0.0995		0.38 [0.03, 4.86], 0.4393		0.22 [0.04, 1.25], 0.0707	
RD [95%-CI]; p-value	-0.32 [-0.78, 0.13], 0.1623		-0.14 [-0.58, 0.30], 0.5367		-0.23 [-0.56, 0.09], 0.1552	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	19/102 (18.6)	8/57 (14.0)	9/92 (9.8)	6/56 (10.7)	28/194 (14.4)	14/113 (12.4)
RR [95%-CI]; p-value	1.33 [0.62, 2.84], 0.4653		0.91 [0.34, 2.43], 0.8554		1.16 [0.64, 2.12], 0.6169	
OR [95%-CI]; p-value	1.40 [0.57, 3.44], 0.4595		0.90 [0.30, 2.69], 0.8555		1.19 [0.60, 2.37], 0.6153	
RD [95%-CI]; p-value	0.05 [-0.07, 0.16], 0.4442		-0.01 [-0.11, 0.09], 0.8568		0.02 [-0.06, 0.10], 0.6091	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.5256		0.1360		0.2500	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	8/102 (7.8)	3/57 (5.3)	5/92 (5.4)	0/56 (0.0)	13/194 (6.7)	3/113 (2.7)
RR [95%-CI]; p-value	1.49 [0.41, 5.40], 0.5434		6.14 [0.34, 110.30], 0.2181		2.52 [0.73, 8.67], 0.1413	
OR [95%-CI]; p-value	1.53 [0.39, 6.02], 0.5387		6.44 [0.34, 120.12], 0.1541		2.63 [0.73, 9.45], 0.1240	
RD [95%-CI]; p-value	0.03 [-0.05, 0.10], 0.5167		0.05 [-0.01, 0.10], 0.0886		0.04 [-0.01, 0.09], 0.0848	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.8948		NA		0.7070	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	1/102 (1.0)	1/57 (1.8)	0/92 (0.0)	0/56 (0.0)	1/194 (0.5)	1/113 (0.9)
RR [95%-CI]; p-value	0.56 [0.04, 8.77], 0.6786		NA		0.58 [0.04, 9.22], 0.7013	
OR [95%-CI]; p-value	0.55 [0.03, 9.04], 0.6745		NA		0.58 [0.04, 9.37], 0.6979	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.6979		NA		-0.00 [-0.02, 0.02], 0.7172	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.6685		NA		0.5263	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	1/5 (20.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	0.19 [0.01, 4.71], 0.3071		NA		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	0.15 [0.00, 5.49], 0.2541		NA		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	-0.16 [-0.53, 0.20], 0.3813		NA		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	0/102 (0.0)	0/57 (0.0)	0/92 (0.0)	0/56 (0.0)	0/194 (0.0)	0/113 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.2456		0.0222		0.0015	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	7/13 (53.8)	5/5 (100.0)	9/27 (33.3)	3/4 (75.0)	16/40 (40.0)	8/9 (88.9)
RR [95%-CI]; p-value	0.59 [0.34, 1.05], 0.0710		0.44 [0.20, 0.97], 0.0410		0.45 [0.29, 0.70], 0.0004	
OR [95%-CI]; p-value	0.12 [0.01, 2.60], 0.1269		0.17 [0.02, 1.84], 0.1103		0.08 [0.01, 0.73], 0.0080	
RD [95%-CI]; p-value	-0.37 [-0.73, -0.01], 0.0449		-0.42 [-0.88, 0.04], 0.0759		-0.49 [-0.74, -0.23], 0.0002	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	61/102 (59.8)	40/57 (70.2)	51/92 (55.4)	26/56 (46.4)	112/194 (57.7)	66/113 (58.4)
RR [95%-CI]; p-value	0.85 [0.68, 1.08], 0.1772		1.19 [0.85, 1.67], 0.3007		0.99 [0.81, 1.20], 0.9078	
OR [95%-CI]; p-value	0.63 [0.32, 1.26], 0.1926		1.44 [0.74, 2.80], 0.2875		0.97 [0.61, 1.56], 0.9080	
RD [95%-CI]; p-value	-0.10 [-0.26, 0.05], 0.1816		0.09 [-0.08, 0.26], 0.2860		-0.01 [-0.12, 0.11], 0.9079	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.6168		0.9648		0.7795	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	8/27 (29.6)	1/4 (25.0)	11/40 (27.5)	3/9 (33.3)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		1.19 [0.20, 7.13], 0.8528		0.83 [0.29, 2.36], 0.7201	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		1.26 [0.11, 14.05], 0.8490		0.76 [0.16, 3.57], 0.7263	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		0.05 [-0.41, 0.50], 0.8429		-0.06 [-0.40, 0.28], 0.7349	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	35/102 (34.3)	23/57 (40.4)	28/92 (30.4)	15/56 (26.8)	63/194 (32.5)	38/113 (33.6)
RR [95%-CI]; p-value	0.85 [0.56, 1.29], 0.4434		1.14 [0.67, 1.93], 0.6379		0.97 [0.69, 1.34], 0.8352	
OR [95%-CI]; p-value	0.77 [0.40, 1.51], 0.4482		1.20 [0.57, 2.51], 0.6353		0.95 [0.58, 1.55], 0.8356	
RD [95%-CI]; p-value	-0.06 [-0.22, 0.10], 0.4516		0.04 [-0.11, 0.19], 0.6319		-0.01 [-0.12, 0.10], 0.8359	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s7.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.0314		0.6968		0.0518	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		NA		0.06 [0.00, 1.13], 0.0601	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		NA		0.04 [0.00, 1.07], 0.0093	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		NA		-0.21 [-0.48, 0.06], 0.1329	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	12/102 (11.8)	2/57 (3.5)	3/92 (3.3)	5/56 (8.9)	15/194 (7.7)	7/113 (6.2)
RR [95%-CI]; p-value	3.35 [0.78, 14.46], 0.1047		0.37 [0.09, 1.47], 0.1562		1.25 [0.52, 2.97], 0.6161	
OR [95%-CI]; p-value	3.67 [0.79, 17.00], 0.0781		0.34 [0.08, 1.50], 0.1392		1.27 [0.50, 3.21], 0.6145	
RD [95%-CI]; p-value	0.08 [0.00, 0.16], 0.0397		-0.06 [-0.14, 0.03], 0.1810		0.02 [-0.04, 0.07], 0.6047	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_3_1_m_sf_ttl_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.2188		0.3548		0.0919	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	1/27 (3.7)	0/4 (0.0)	1/40 (2.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.33 [0.01, 8.55], 0.5069		0.11 [0.01, 1.11], 0.0614	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.31 [0.01, 10.76], 0.4945		0.09 [0.01, 1.13], 0.0258	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.07 [-0.37, 0.22], 0.6273		-0.20 [-0.47, 0.08], 0.1612	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	8/102 (7.8)	7/57 (12.3)	6/92 (6.5)	2/56 (3.6)	14/194 (7.2)	9/113 (8.0)
RR [95%-CI]; p-value	0.64 [0.24, 1.67], 0.3606		1.83 [0.38, 8.74], 0.4509		0.91 [0.41, 2.03], 0.8101	
OR [95%-CI]; p-value	0.61 [0.21, 1.77], 0.3586		1.88 [0.37, 9.67], 0.4414		0.90 [0.38, 2.15], 0.8102	
RD [95%-CI]; p-value	-0.04 [-0.14, 0.06], 0.3840		0.03 [-0.04, 0.10], 0.4091		-0.01 [-0.07, 0.05], 0.8124	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6898		0.4224		0.7715	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	6/27 (22.2)	1/4 (25.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.89 [0.14, 5.59], 0.9001		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.86 [0.07, 9.82], 0.9013		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.03 [-0.48, 0.42], 0.9042		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	20/102 (19.6)	17/57 (29.8)	17/92 (18.5)	5/56 (8.9)	37/194 (19.1)	22/113 (19.5)
RR [95%-CI]; p-value	0.66 [0.38, 1.15], 0.1417		2.07 [0.81, 5.30], 0.1294		0.98 [0.61, 1.57], 0.9321	
OR [95%-CI]; p-value	0.57 [0.27, 1.21], 0.1437		2.31 [0.80, 6.66], 0.1132		0.97 [0.54, 1.75], 0.9322	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.04], 0.1572		0.10 [-0.01, 0.20], 0.0858		-0.00 [-0.10, 0.09], 0.9323	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.2048		0.2380		0.0520	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	2/27 (7.4)	1/4 (25.0)	2/40 (5.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.30 [0.03, 2.57], 0.2694		0.15 [0.03, 0.77], 0.0231	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.24 [0.02, 3.51], 0.2667		0.11 [0.01, 0.77], 0.0112	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.18 [-0.61, 0.26], 0.4287		-0.28 [-0.60, 0.03], 0.0782	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	15/102 (14.7)	13/57 (22.8)	12/92 (13.0)	6/56 (10.7)	27/194 (13.9)	19/113 (16.8)
RR [95%-CI]; p-value	0.64 [0.33, 1.26], 0.1981		1.22 [0.48, 3.06], 0.6758		0.83 [0.48, 1.42], 0.4919	
OR [95%-CI]; p-value	0.58 [0.26, 1.33], 0.1984		1.25 [0.44, 3.54], 0.6742		0.80 [0.42, 1.52], 0.4928	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2177		0.02 [-0.08, 0.13], 0.6676		-0.03 [-0.11, 0.06], 0.5013	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.4561		0.7089		0.3445	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	5/27 (18.5)	1/4 (25.0)	8/40 (20.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		0.74 [0.11, 4.82], 0.7535		0.60 [0.20, 1.83], 0.3682	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		0.68 [0.06, 8.00], 0.7594		0.50 [0.10, 2.45], 0.3864	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		-0.06 [-0.51, 0.38], 0.7772		-0.13 [-0.47, 0.20], 0.4312	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	28/102 (27.5)	15/57 (26.3)	23/92 (25.0)	13/56 (23.2)	51/194 (26.3)	28/113 (24.8)
RR [95%-CI]; p-value	1.04 [0.61, 1.78], 0.8775		1.08 [0.59, 1.95], 0.8066		1.06 [0.71, 1.58], 0.7711	
OR [95%-CI]; p-value	1.06 [0.51, 2.20], 0.8772		1.10 [0.51, 2.40], 0.8060		1.08 [0.64, 1.85], 0.7704	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8767		0.02 [-0.12, 0.16], 0.8048		0.02 [-0.09, 0.12], 0.7692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.7399		0.7681		0.9759	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	4/27 (14.8)	0/4 (0.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		1.33 [0.08, 21.18], 0.8384		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		1.39 [0.06, 31.69], 0.8353		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		0.04 [-0.28, 0.36], 0.8204		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	8/57 (14.0)	7/92 (7.6)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.77 [0.33, 1.80], 0.5440		0.85 [0.28, 2.56], 0.7753		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.74 [0.28, 1.96], 0.5445		0.84 [0.25, 2.79], 0.7754		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.5568		-0.01 [-0.11, 0.08], 0.7792		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0212		0.0518		0.0003	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	5/5 (100.0)	3/27 (11.1)	2/4 (50.0)	4/40 (10.0)	7/9 (77.8)
RR [95%-CI]; p-value	0.08 [0.01, 0.57], 0.0109		0.22 [0.05, 0.95], 0.0419		0.13 [0.05, 0.35], <0.0001	
OR [95%-CI]; p-value	0.01 [0.00, 0.29], 0.0005		0.13 [0.01, 1.24], 0.0484		0.03 [0.00, 0.21], <0.0001	
RD [95%-CI]; p-value	-0.83 [-1.00, -0.55], <0.0001		-0.39 [-0.89, 0.12], 0.1305		-0.68 [-0.96, -0.39], <0.0001	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	22/102 (21.6)	14/57 (24.6)	18/92 (19.6)	10/56 (17.9)	40/194 (20.6)	24/113 (21.2)
RR [95%-CI]; p-value	0.88 [0.49, 1.58], 0.6641		1.10 [0.55, 2.20], 0.7976		0.97 [0.62, 1.52], 0.8972	
OR [95%-CI]; p-value	0.84 [0.39, 1.82], 0.6654		1.12 [0.48, 2.63], 0.7969		0.96 [0.55, 1.70], 0.8973	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6693		0.02 [-0.11, 0.15], 0.7952		-0.01 [-0.10, 0.09], 0.8976	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.6775		0.8376		0.8733	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	3/27 (11.1)	0/4 (0.0)	5/40 (12.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		1.00 [0.06, 16.82], 1.0000		0.56 [0.13, 2.45], 0.4436	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		1.00 [0.04, 23.94], 1.0000		0.50 [0.08, 3.12], 0.4514	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		0.00 [-0.31, 0.31], 1.0000		-0.10 [-0.39, 0.19], 0.5116	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	18/102 (17.6)	18/57 (31.6)	17/92 (18.5)	14/56 (25.0)	35/194 (18.0)	32/113 (28.3)
RR [95%-CI]; p-value	0.56 [0.32, 0.99], 0.0444		0.74 [0.40, 1.38], 0.3428		0.64 [0.42, 0.97], 0.0352	
OR [95%-CI]; p-value	0.46 [0.22, 0.99], 0.0441		0.68 [0.30, 1.52], 0.3444		0.56 [0.32, 0.96], 0.0355	
RD [95%-CI]; p-value	-0.14 [-0.28, 0.00], 0.0537		-0.07 [-0.20, 0.07], 0.3557		-0.10 [-0.20, -0.00], 0.0422	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.4803		0.1299		0.0962	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	1/5 (20.0)	1/27 (3.7)	1/4 (25.0)	1/40 (2.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.19 [0.01, 4.71], 0.3071		0.15 [0.01, 1.93], 0.1446		0.11 [0.01, 1.11], 0.0614	
OR [95%-CI]; p-value	0.15 [0.00, 5.49], 0.2541		0.12 [0.01, 2.36], 0.1057		0.09 [0.01, 1.13], 0.0258	
RD [95%-CI]; p-value	-0.16 [-0.53, 0.20], 0.3813		-0.21 [-0.64, 0.22], 0.3320		-0.20 [-0.47, 0.08], 0.1612	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	10/57 (17.5)	12/92 (13.0)	6/56 (10.7)	23/194 (11.9)	16/113 (14.2)
RR [95%-CI]; p-value	0.61 [0.28, 1.36], 0.2289		1.22 [0.48, 3.06], 0.6758		0.84 [0.46, 1.52], 0.5582	
OR [95%-CI]; p-value	0.57 [0.23, 1.43], 0.2273		1.25 [0.44, 3.54], 0.6742		0.82 [0.41, 1.62], 0.5589	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.05], 0.2519		0.02 [-0.08, 0.13], 0.6676		-0.02 [-0.10, 0.06], 0.5664	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3333		0.0582		0.0439	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.07 [0.00, 1.84], 0.1116		0.04 [0.00, 0.68], 0.0262	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.06 [0.00, 2.03], 0.0419		0.03 [0.00, 0.56], 0.0007	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.23 [-0.66, 0.20], 0.2876		-0.32 [-0.63, -0.01], 0.0423	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	4/102 (3.9)	5/57 (8.8)	5/92 (5.4)	1/56 (1.8)	9/194 (4.6)	6/113 (5.3)
RR [95%-CI]; p-value	0.45 [0.13, 1.60], 0.2156		3.04 [0.36, 25.39], 0.3038		0.87 [0.32, 2.39], 0.7927	
OR [95%-CI]; p-value	0.42 [0.11, 1.65], 0.2044		3.16 [0.36, 27.78], 0.2750		0.87 [0.30, 2.50], 0.7927	
RD [95%-CI]; p-value	-0.05 [-0.13, 0.03], 0.2494		0.04 [-0.02, 0.09], 0.2165		-0.01 [-0.06, 0.04], 0.7960	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3645		0.4617		0.2116	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	4/27 (14.8)	1/4 (25.0)	6/40 (15.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		0.59 [0.09, 4.06], 0.5939		0.45 [0.14, 1.47], 0.1856	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		0.52 [0.04, 6.36], 0.6052		0.35 [0.07, 1.81], 0.1994	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		-0.10 [-0.55, 0.34], 0.6537		-0.18 [-0.51, 0.14], 0.2722	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	13/102 (12.7)	8/57 (14.0)	9/92 (9.8)	4/56 (7.1)	22/194 (11.3)	12/113 (10.6)
RR [95%-CI]; p-value	0.91 [0.40, 2.06], 0.8175		1.37 [0.44, 4.24], 0.5854		1.07 [0.55, 2.07], 0.8463	
OR [95%-CI]; p-value	0.89 [0.35, 2.31], 0.8178		1.41 [0.41, 4.81], 0.5822		1.08 [0.51, 2.27], 0.8461	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.10], 0.8198		0.03 [-0.06, 0.12], 0.5686		0.01 [-0.07, 0.08], 0.8450	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9887		0.0816		0.2511	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	NA		0.07 [0.00, 1.84], 0.1116		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	NA		0.06 [0.00, 2.03], 0.0419		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	NA		-0.23 [-0.66, 0.20], 0.2876		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	6/102 (5.9)	8/57 (14.0)	12/92 (13.0)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.42 [0.15, 1.15], 0.0908		1.46 [0.54, 3.93], 0.4525		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.38 [0.13, 1.17], 0.0819		1.53 [0.51, 4.60], 0.4464		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.08 [-0.18, 0.02], 0.1139		0.04 [-0.06, 0.14], 0.4271		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.1.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.6758		0.0604		0.1503	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	0/27 (0.0)	2/4 (50.0)	3/40 (7.5)	3/9 (33.3)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.04 [0.00, 0.67], 0.0259		0.23 [0.05, 0.94], 0.0406	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.02 [0.00, 0.56], 0.0009		0.16 [0.03, 1.00], 0.0327	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.48 [-0.97, 0.01], 0.0552		-0.26 [-0.58, 0.06], 0.1120	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	9/102 (8.8)	7/57 (12.3)	6/92 (6.5)	5/56 (8.9)	15/194 (7.7)	12/113 (10.6)
RR [95%-CI]; p-value	0.72 [0.28, 1.83], 0.4874		0.73 [0.23, 2.28], 0.5890		0.73 [0.35, 1.50], 0.3895	
OR [95%-CI]; p-value	0.69 [0.24, 1.97], 0.4871		0.71 [0.21, 2.45], 0.5882		0.71 [0.32, 1.57], 0.3889	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5041		-0.02 [-0.11, 0.07], 0.6007		-0.03 [-0.10, 0.04], 0.4060	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_1_m_soc_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.3.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5249		0.1886		0.9615	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	2/40 (5.0)	1/9 (11.1)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.33 [0.01, 8.55], 0.5069		0.45 [0.05, 4.44], 0.4941	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.31 [0.01, 10.76], 0.4945		0.42 [0.03, 5.23], 0.4896	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.07 [-0.37, 0.22], 0.6273		-0.06 [-0.28, 0.16], 0.5795	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	3/102 (2.9)	11/57 (19.3)	5/92 (5.4)	0/56 (0.0)	8/194 (4.1)	11/113 (9.7)
RR [95%-CI]; p-value	0.15 [0.04, 0.52], 0.0028		6.14 [0.34, 110.30], 0.2181		0.42 [0.18, 1.02], 0.0559	
OR [95%-CI]; p-value	0.13 [0.03, 0.48], 0.0005		6.44 [0.34, 120.12], 0.1541		0.40 [0.16, 1.02], 0.0491	
RD [95%-CI]; p-value	-0.16 [-0.27, -0.06], 0.0029		0.05 [-0.01, 0.10], 0.0886		-0.06 [-0.12, 0.01], 0.0733	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_3_m_pt_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.3.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.7742		0.3548		0.3050	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	2/5 (40.0)	1/27 (3.7)	0/4 (0.0)	2/40 (5.0)	2/9 (22.2)
RR [95%-CI]; p-value	0.19 [0.02, 1.68], 0.1360		0.33 [0.01, 8.55], 0.5069		0.23 [0.04, 1.39], 0.1085	
OR [95%-CI]; p-value	0.13 [0.01, 1.89], 0.0995		0.31 [0.01, 10.76], 0.4945		0.18 [0.02, 1.53], 0.0882	
RD [95%-CI]; p-value	-0.32 [-0.78, 0.13], 0.1623		-0.07 [-0.37, 0.22], 0.6273		-0.17 [-0.45, 0.11], 0.2278	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	3/102 (2.9)	6/57 (10.5)	6/92 (6.5)	2/56 (3.6)	9/194 (4.6)	8/113 (7.1)
RR [95%-CI]; p-value	0.28 [0.07, 1.08], 0.0636		1.83 [0.38, 8.74], 0.4509		0.66 [0.26, 1.65], 0.3698	
OR [95%-CI]; p-value	0.26 [0.06, 1.07], 0.0472		1.88 [0.37, 9.67], 0.4414		0.64 [0.24, 1.70], 0.3672	
RD [95%-CI]; p-value	-0.08 [-0.16, 0.01], 0.0844		0.03 [-0.04, 0.10], 0.4091		-0.02 [-0.08, 0.03], 0.3912	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_3_m_pt_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.3.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.7742		0.0855		0.0750	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	1/5 (20.0)	0/27 (0.0)	2/4 (50.0)	2/40 (5.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.77 [0.09, 6.72], 0.8125		0.04 [0.00, 0.67], 0.0259		0.15 [0.03, 0.77], 0.0231	
OR [95%-CI]; p-value	0.73 [0.05, 10.39], 0.8139		0.02 [0.00, 0.56], 0.0009		0.11 [0.01, 0.77], 0.0112	
RD [95%-CI]; p-value	-0.05 [-0.45, 0.36], 0.8218		-0.48 [-0.97, 0.01], 0.0552		-0.28 [-0.60, 0.03], 0.0782	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	6/102 (5.9)	3/57 (5.3)	4/92 (4.3)	4/56 (7.1)	10/194 (5.2)	7/113 (6.2)
RR [95%-CI]; p-value	1.12 [0.29, 4.30], 0.8715		0.61 [0.16, 2.34], 0.4696		0.83 [0.33, 2.13], 0.7008	
OR [95%-CI]; p-value	1.13 [0.27, 4.68], 0.8713		0.59 [0.14, 2.46], 0.4658		0.82 [0.30, 2.23], 0.7008	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8694		-0.03 [-0.11, 0.05], 0.4896		-0.01 [-0.06, 0.04], 0.7071	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_3_m_pt_ae10pct_dose_pp.sas using SAS 9.4

Table 12.4.8.1.1.s7.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6586		0.2684		0.2940	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	NA		0.07 [0.00, 1.84], 0.1116		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	NA		0.06 [0.00, 2.03], 0.0419		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	NA		-0.23 [-0.66, 0.20], 0.2876		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	2/102 (2.0)	1/57 (1.8)	2/92 (2.2)	2/56 (3.6)	4/194 (2.1)	3/113 (2.7)
RR [95%-CI]; p-value	1.12 [0.10, 12.06], 0.9270		0.61 [0.09, 4.20], 0.6145		0.78 [0.18, 3.41], 0.7376	
OR [95%-CI]; p-value	1.12 [0.10, 12.63], 0.9269		0.60 [0.08, 4.38], 0.6111		0.77 [0.17, 3.51], 0.7371	
RD [95%-CI]; p-value	0.00 [-0.04, 0.05], 0.9258		-0.01 [-0.07, 0.04], 0.6309		-0.01 [-0.04, 0.03], 0.7451	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_8_1_1_m_soc_sae5pct_dose_pp.sas using SAS 9.4

Table 12.4.8.1.2.s7.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_8_1_2_m_pt_sae5pct_dose_pp.sas using SAS 9.4

Table 12.4.5.1.1.s7.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_5_1_1_m_soc_aeg35pct_dose_pp.sas using SAS 9.4

Table 12.4.5.1.2.s7.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_5_1_2_m_pt_aeg35pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6898		0.4224		0.7715	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	6/27 (22.2)	1/4 (25.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.89 [0.14, 5.59], 0.9001		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.86 [0.07, 9.82], 0.9013		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.03 [-0.48, 0.42], 0.9042		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	20/102 (19.6)	17/57 (29.8)	17/92 (18.5)	5/56 (8.9)	37/194 (19.1)	22/113 (19.5)
RR [95%-CI]; p-value	0.66 [0.38, 1.15], 0.1417		2.07 [0.81, 5.30], 0.1294		0.98 [0.61, 1.57], 0.9321	
OR [95%-CI]; p-value	0.57 [0.27, 1.21], 0.1437		2.31 [0.80, 6.66], 0.1132		0.97 [0.54, 1.75], 0.9322	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.04], 0.1572		0.10 [-0.01, 0.20], 0.0858		-0.00 [-0.10, 0.09], 0.9323	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.2048		0.2380		0.0520	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	2/5 (40.0)	2/27 (7.4)	1/4 (25.0)	2/40 (5.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.09 [0.00, 1.72], 0.1107		0.30 [0.03, 2.57], 0.2694		0.15 [0.03, 0.77], 0.0231	
OR [95%-CI]; p-value	0.06 [0.00, 1.63], 0.0426		0.24 [0.02, 3.51], 0.2667		0.11 [0.01, 0.77], 0.0112	
RD [95%-CI]; p-value	-0.36 [-0.80, 0.08], 0.1068		-0.18 [-0.61, 0.26], 0.4287		-0.28 [-0.60, 0.03], 0.0782	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	15/102 (14.7)	13/57 (22.8)	12/92 (13.0)	6/56 (10.7)	27/194 (13.9)	19/113 (16.8)
RR [95%-CI]; p-value	0.64 [0.33, 1.26], 0.1981		1.22 [0.48, 3.06], 0.6758		0.83 [0.48, 1.42], 0.4919	
OR [95%-CI]; p-value	0.58 [0.26, 1.33], 0.1984		1.25 [0.44, 3.54], 0.6742		0.80 [0.42, 1.52], 0.4928	
RD [95%-CI]; p-value	-0.08 [-0.21, 0.05], 0.2177		0.02 [-0.08, 0.13], 0.6676		-0.03 [-0.11, 0.06], 0.5013	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.4561		0.7089		0.3445	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	5/27 (18.5)	1/4 (25.0)	8/40 (20.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		0.74 [0.11, 4.82], 0.7535		0.60 [0.20, 1.83], 0.3682	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		0.68 [0.06, 8.00], 0.7594		0.50 [0.10, 2.45], 0.3864	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		-0.06 [-0.51, 0.38], 0.7772		-0.13 [-0.47, 0.20], 0.4312	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	28/102 (27.5)	15/57 (26.3)	23/92 (25.0)	13/56 (23.2)	51/194 (26.3)	28/113 (24.8)
RR [95%-CI]; p-value	1.04 [0.61, 1.78], 0.8775		1.08 [0.59, 1.95], 0.8066		1.06 [0.71, 1.58], 0.7711	
OR [95%-CI]; p-value	1.06 [0.51, 2.20], 0.8772		1.10 [0.51, 2.40], 0.8060		1.08 [0.64, 1.85], 0.7704	
RD [95%-CI]; p-value	0.01 [-0.13, 0.15], 0.8767		0.02 [-0.12, 0.16], 0.8048		0.02 [-0.09, 0.12], 0.7692	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.8726		0.5526		0.9650	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	3/40 (7.5)	0/9 (0.0)
RR [95%-CI]; p-value	0.85 [0.03, 21.72], 0.9196		0.67 [0.04, 12.53], 0.7865		1.43 [0.08, 26.14], 0.8114	
OR [95%-CI]; p-value	0.83 [0.02, 29.05], 0.9198		0.64 [0.02, 16.90], 0.7879		1.46 [0.07, 31.79], 0.8090	
RD [95%-CI]; p-value	-0.01 [-0.29, 0.27], 0.9222		-0.04 [-0.34, 0.27], 0.8129		0.02 [-0.14, 0.19], 0.7889	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	10/102 (9.8)	5/57 (8.8)	6/92 (6.5)	2/56 (3.6)	16/194 (8.2)	7/113 (6.2)
RR [95%-CI]; p-value	1.12 [0.40, 3.11], 0.8313		1.83 [0.38, 8.74], 0.4509		1.33 [0.56, 3.14], 0.5129	
OR [95%-CI]; p-value	1.13 [0.37, 3.49], 0.8309		1.88 [0.37, 9.67], 0.4414		1.36 [0.54, 3.42], 0.5100	
RD [95%-CI]; p-value	0.01 [-0.08, 0.10], 0.8286		0.03 [-0.04, 0.10], 0.4091		0.02 [-0.04, 0.08], 0.4949	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.7399		0.7681		0.9759	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	2/5 (40.0)	4/27 (14.8)	0/4 (0.0)	7/40 (17.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.58 [0.13, 2.49], 0.4609		1.33 [0.08, 21.18], 0.8384		0.79 [0.20, 3.18], 0.7372	
OR [95%-CI]; p-value	0.45 [0.05, 4.09], 0.4728		1.39 [0.06, 31.69], 0.8353		0.74 [0.13, 4.36], 0.7410	
RD [95%-CI]; p-value	-0.17 [-0.66, 0.32], 0.4955		0.04 [-0.28, 0.36], 0.8204		-0.05 [-0.34, 0.25], 0.7546	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	8/57 (14.0)	7/92 (7.6)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.77 [0.33, 1.80], 0.5440		0.85 [0.28, 2.56], 0.7753		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.74 [0.28, 1.96], 0.5445		0.84 [0.25, 2.79], 0.7754		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.08], 0.5568		-0.01 [-0.11, 0.08], 0.7792		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.0212		0.0518		0.0003	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	5/5 (100.0)	3/27 (11.1)	2/4 (50.0)	4/40 (10.0)	7/9 (77.8)
RR [95%-CI]; p-value	0.08 [0.01, 0.57], 0.0109		0.22 [0.05, 0.95], 0.0419		0.13 [0.05, 0.35], <0.0001	
OR [95%-CI]; p-value	0.01 [0.00, 0.29], 0.0005		0.13 [0.01, 1.24], 0.0484		0.03 [0.00, 0.21], <0.0001	
RD [95%-CI]; p-value	-0.83 [-1.00, -0.55], <0.0001		-0.39 [-0.89, 0.12], 0.1305		-0.68 [-0.96, -0.39], <0.0001	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	22/102 (21.6)	14/57 (24.6)	18/92 (19.6)	10/56 (17.9)	40/194 (20.6)	24/113 (21.2)
RR [95%-CI]; p-value	0.88 [0.49, 1.58], 0.6641		1.10 [0.55, 2.20], 0.7976		0.97 [0.62, 1.52], 0.8972	
OR [95%-CI]; p-value	0.84 [0.39, 1.82], 0.6654		1.12 [0.48, 2.63], 0.7969		0.96 [0.55, 1.70], 0.8973	
RD [95%-CI]; p-value	-0.03 [-0.17, 0.11], 0.6693		0.02 [-0.11, 0.15], 0.7952		-0.01 [-0.10, 0.09], 0.8976	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.6775		0.8376		0.8733	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	3/27 (11.1)	0/4 (0.0)	5/40 (12.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		1.00 [0.06, 16.82], 1.0000		0.56 [0.13, 2.45], 0.4436	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		1.00 [0.04, 23.94], 1.0000		0.50 [0.08, 3.12], 0.4514	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		0.00 [-0.31, 0.31], 1.0000		-0.10 [-0.39, 0.19], 0.5116	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	18/102 (17.6)	18/57 (31.6)	17/92 (18.5)	14/56 (25.0)	35/194 (18.0)	32/113 (28.3)
RR [95%-CI]; p-value	0.56 [0.32, 0.99], 0.0444		0.74 [0.40, 1.38], 0.3428		0.64 [0.42, 0.97], 0.0352	
OR [95%-CI]; p-value	0.46 [0.22, 0.99], 0.0441		0.68 [0.30, 1.52], 0.3444		0.56 [0.32, 0.96], 0.0355	
RD [95%-CI]; p-value	-0.14 [-0.28, 0.00], 0.0537		-0.07 [-0.20, 0.07], 0.3557		-0.10 [-0.20, -0.00], 0.0422	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.4803		0.1299		0.0962	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	1/5 (20.0)	1/27 (3.7)	1/4 (25.0)	1/40 (2.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.19 [0.01, 4.71], 0.3071		0.15 [0.01, 1.93], 0.1446		0.11 [0.01, 1.11], 0.0614	
OR [95%-CI]; p-value	0.15 [0.00, 5.49], 0.2541		0.12 [0.01, 2.36], 0.1057		0.09 [0.01, 1.13], 0.0258	
RD [95%-CI]; p-value	-0.16 [-0.53, 0.20], 0.3813		-0.21 [-0.64, 0.22], 0.3320		-0.20 [-0.47, 0.08], 0.1612	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	11/102 (10.8)	10/57 (17.5)	12/92 (13.0)	6/56 (10.7)	23/194 (11.9)	16/113 (14.2)
RR [95%-CI]; p-value	0.61 [0.28, 1.36], 0.2289		1.22 [0.48, 3.06], 0.6758		0.84 [0.46, 1.52], 0.5582	
OR [95%-CI]; p-value	0.57 [0.23, 1.43], 0.2273		1.25 [0.44, 3.54], 0.6742		0.82 [0.41, 1.62], 0.5589	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.05], 0.2519		0.02 [-0.08, 0.13], 0.6676		-0.02 [-0.10, 0.06], 0.5664	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3645		0.4617		0.2116	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	2/13 (15.4)	2/5 (40.0)	4/27 (14.8)	1/4 (25.0)	6/40 (15.0)	3/9 (33.3)
RR [95%-CI]; p-value	0.38 [0.07, 2.04], 0.2611		0.59 [0.09, 4.06], 0.5939		0.45 [0.14, 1.47], 0.1856	
OR [95%-CI]; p-value	0.27 [0.03, 2.83], 0.2605		0.52 [0.04, 6.36], 0.6052		0.35 [0.07, 1.81], 0.1994	
RD [95%-CI]; p-value	-0.25 [-0.72, 0.23], 0.3068		-0.10 [-0.55, 0.34], 0.6537		-0.18 [-0.51, 0.14], 0.2722	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	13/102 (12.7)	8/57 (14.0)	9/92 (9.8)	4/56 (7.1)	22/194 (11.3)	12/113 (10.6)
RR [95%-CI]; p-value	0.91 [0.40, 2.06], 0.8175		1.37 [0.44, 4.24], 0.5854		1.07 [0.55, 2.07], 0.8463	
OR [95%-CI]; p-value	0.89 [0.35, 2.31], 0.8178		1.41 [0.41, 4.81], 0.5822		1.08 [0.51, 2.27], 0.8461	
RD [95%-CI]; p-value	-0.01 [-0.12, 0.10], 0.8198		0.03 [-0.06, 0.12], 0.5686		0.01 [-0.07, 0.08], 0.8450	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.9887		0.0816		0.2511	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	1/4 (25.0)	0/40 (0.0)	1/9 (11.1)
RR [95%-CI]; p-value	NA		0.07 [0.00, 1.84], 0.1116		0.11 [0.00, 3.06], 0.1942	
OR [95%-CI]; p-value	NA		0.06 [0.00, 2.03], 0.0419		0.10 [0.00, 3.24], 0.1179	
RD [95%-CI]; p-value	NA		-0.23 [-0.66, 0.20], 0.2876		-0.10 [-0.31, 0.11], 0.3523	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	6/102 (5.9)	8/57 (14.0)	12/92 (13.0)	5/56 (8.9)	18/194 (9.3)	13/113 (11.5)
RR [95%-CI]; p-value	0.42 [0.15, 1.15], 0.0908		1.46 [0.54, 3.93], 0.4525		0.81 [0.41, 1.58], 0.5321	
OR [95%-CI]; p-value	0.38 [0.13, 1.17], 0.0819		1.53 [0.51, 4.60], 0.4464		0.79 [0.37, 1.67], 0.5324	
RD [95%-CI]; p-value	-0.08 [-0.18, 0.02], 0.1139		0.04 [-0.06, 0.14], 0.4271		-0.02 [-0.09, 0.05], 0.5423	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.2.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.6758		0.0604		0.1503	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	0/27 (0.0)	2/4 (50.0)	3/40 (7.5)	3/9 (33.3)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.04 [0.00, 0.67], 0.0259		0.23 [0.05, 0.94], 0.0406	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.02 [0.00, 0.56], 0.0009		0.16 [0.03, 1.00], 0.0327	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.48 [-0.97, 0.01], 0.0552		-0.26 [-0.58, 0.06], 0.1120	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	9/102 (8.8)	7/57 (12.3)	6/92 (6.5)	5/56 (8.9)	15/194 (7.7)	12/113 (10.6)
RR [95%-CI]; p-value	0.72 [0.28, 1.83], 0.4874		0.73 [0.23, 2.28], 0.5890		0.73 [0.35, 1.50], 0.3895	
OR [95%-CI]; p-value	0.69 [0.24, 1.97], 0.4871		0.71 [0.21, 2.45], 0.5882		0.71 [0.32, 1.57], 0.3889	
RD [95%-CI]; p-value	-0.03 [-0.14, 0.07], 0.5041		-0.02 [-0.11, 0.07], 0.6007		-0.03 [-0.10, 0.04], 0.4060	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_2_m_soc_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.4.s7.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.5249		0.1886		0.9615	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	2/40 (5.0)	1/9 (11.1)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.33 [0.01, 8.55], 0.5069		0.45 [0.05, 4.44], 0.4941	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.31 [0.01, 10.76], 0.4945		0.42 [0.03, 5.23], 0.4896	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.07 [-0.37, 0.22], 0.6273		-0.06 [-0.28, 0.16], 0.5795	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	3/102 (2.9)	11/57 (19.3)	5/92 (5.4)	0/56 (0.0)	8/194 (4.1)	11/113 (9.7)
RR [95%-CI]; p-value	0.15 [0.04, 0.52], 0.0028		6.14 [0.34, 110.30], 0.2181		0.42 [0.18, 1.02], 0.0559	
OR [95%-CI]; p-value	0.13 [0.03, 0.48], 0.0005		6.44 [0.34, 120.12], 0.1541		0.40 [0.16, 1.02], 0.0491	
RD [95%-CI]; p-value	-0.16 [-0.27, -0.06], 0.0029		0.05 [-0.01, 0.10], 0.0886		-0.06 [-0.12, 0.01], 0.0733	

Abbreviations: CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_4_m_pt_ae1pct_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.3561		0.7328		0.7705	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	4/40 (10.0)	1/9 (11.1)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.33 [0.01, 8.55], 0.5069		0.90 [0.11, 7.12], 0.9205	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.31 [0.01, 10.76], 0.4945		0.89 [0.09, 9.06], 0.9207	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.07 [-0.37, 0.22], 0.6273		-0.01 [-0.24, 0.21], 0.9230	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	8/102 (7.8)	1/57 (1.8)	5/92 (5.4)	5/56 (8.9)	13/194 (6.7)	6/113 (5.3)
RR [95%-CI]; p-value	4.47 [0.57, 34.85], 0.1529		0.61 [0.18, 2.01], 0.4152		1.26 [0.49, 3.23], 0.6272	
OR [95%-CI]; p-value	4.77 [0.58, 39.12], 0.1111		0.59 [0.16, 2.12], 0.4115		1.28 [0.47, 3.47], 0.6256	
RD [95%-CI]; p-value	0.06 [-0.00, 0.12], 0.0555		-0.03 [-0.12, 0.05], 0.4359		0.01 [-0.04, 0.07], 0.6155	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.6945		NA		0.5394	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	1/102 (1.0)	0/57 (0.0)	0/92 (0.0)	0/56 (0.0)	1/194 (0.5)	0/113 (0.0)
RR [95%-CI]; p-value	1.13 [0.04, 33.09], 0.9445		NA		1.17 [0.04, 34.60], 0.9276	
OR [95%-CI]; p-value	1.13 [0.04, 34.17], 0.9445		NA		1.17 [0.04, 35.18], 0.9275	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9436		NA		0.00 [-0.02, 0.02], 0.9260	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4074		0.7328		0.8242	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	3/13 (23.1)	1/5 (20.0)	1/27 (3.7)	0/4 (0.0)	4/40 (10.0)	1/9 (11.1)
RR [95%-CI]; p-value	1.15 [0.15, 8.65], 0.8893		0.33 [0.01, 8.55], 0.5069		0.90 [0.11, 7.12], 0.9205	
OR [95%-CI]; p-value	1.20 [0.09, 15.26], 0.8882		0.31 [0.01, 10.76], 0.4945		0.89 [0.09, 9.06], 0.9207	
RD [95%-CI]; p-value	0.03 [-0.39, 0.45], 0.8855		-0.07 [-0.37, 0.22], 0.6273		-0.01 [-0.24, 0.21], 0.9230	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	7/102 (6.9)	1/57 (1.8)	5/92 (5.4)	5/56 (8.9)	12/194 (6.2)	6/113 (5.3)
RR [95%-CI]; p-value	3.91 [0.49, 31.00], 0.1966		0.61 [0.18, 2.01], 0.4152		1.16 [0.45, 3.02], 0.7533	
OR [95%-CI]; p-value	4.13 [0.49, 34.42], 0.1576		0.59 [0.16, 2.12], 0.4115		1.18 [0.43, 3.22], 0.7527	
RD [95%-CI]; p-value	0.05 [-0.01, 0.11], 0.0937		-0.03 [-0.12, 0.05], 0.4359		0.01 [-0.04, 0.06], 0.7481	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.2152		0.4366		0.1054	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	0/27 (0.0)	0/4 (0.0)	1/40 (2.5)	1/9 (11.1)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		NA		0.23 [0.02, 3.27], 0.2746	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		NA		0.21 [0.01, 3.63], 0.2381	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		NA		-0.09 [-0.30, 0.12], 0.4237	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	4/102 (3.9)	0/57 (0.0)	1/92 (1.1)	0/56 (0.0)	5/194 (2.6)	0/113 (0.0)
RR [95%-CI]; p-value	4.51 [0.24, 83.80], 0.3124		1.23 [0.04, 36.02], 0.9051		5.85 [0.32, 106.10], 0.2322	
OR [95%-CI]; p-value	4.65 [0.24, 89.62], 0.2637		1.23 [0.04, 37.29], 0.9049		5.98 [0.32, 110.46], 0.1725	
RD [95%-CI]; p-value	0.03 [-0.01, 0.08], 0.1805		0.00 [-0.03, 0.03], 0.9025		0.02 [-0.00, 0.05], 0.0993	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.8316		0.8779		0.8516	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	2/40 (5.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		0.67 [0.04, 12.53], 0.7865		0.95 [0.05, 19.41], 0.9734	
OR [95%-CI]; p-value	NA		0.64 [0.02, 16.90], 0.7879		0.95 [0.04, 22.85], 0.9734	
RD [95%-CI]; p-value	NA		-0.04 [-0.34, 0.27], 0.8129		-0.00 [-0.16, 0.15], 0.9738	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	10/102 (9.8)	9/57 (15.8)	7/92 (7.6)	5/56 (8.9)	17/194 (8.8)	14/113 (12.4)
RR [95%-CI]; p-value	0.62 [0.27, 1.44], 0.2663		0.85 [0.28, 2.56], 0.7753		0.71 [0.36, 1.38], 0.3098	
OR [95%-CI]; p-value	0.58 [0.22, 1.52], 0.2645		0.84 [0.25, 2.79], 0.7754		0.68 [0.32, 1.44], 0.3091	
RD [95%-CI]; p-value	-0.06 [-0.17, 0.05], 0.2900		-0.01 [-0.11, 0.08], 0.7792		-0.04 [-0.11, 0.04], 0.3277	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.6945		0.3794		0.3780	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	1/102 (1.0)	0/57 (0.0)	2/92 (2.2)	1/56 (1.8)	3/194 (1.5)	1/113 (0.9)
RR [95%-CI]; p-value	1.13 [0.04, 33.09], 0.9445		1.22 [0.11, 13.12], 0.8712		1.75 [0.18, 16.60], 0.6270	
OR [95%-CI]; p-value	1.13 [0.04, 34.17], 0.9445		1.22 [0.11, 13.80], 0.8709		1.76 [0.18, 17.12], 0.6221	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9436		0.00 [-0.04, 0.05], 0.8679		0.01 [-0.02, 0.03], 0.5965	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.8735		0.9546		0.7902	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	2/27 (7.4)	0/4 (0.0)	2/40 (5.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		0.67 [0.04, 12.53], 0.7865		0.95 [0.05, 19.41], 0.9734	
OR [95%-CI]; p-value	NA		0.64 [0.02, 16.90], 0.7879		0.95 [0.04, 22.85], 0.9734	
RD [95%-CI]; p-value	NA		-0.04 [-0.34, 0.27], 0.8129		-0.00 [-0.16, 0.15], 0.9738	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	9/102 (8.8)	9/57 (15.8)	6/92 (6.5)	5/56 (8.9)	15/194 (7.7)	14/113 (12.4)
RR [95%-CI]; p-value	0.56 [0.24, 1.33], 0.1874		0.73 [0.23, 2.28], 0.5890		0.62 [0.31, 1.24], 0.1808	
OR [95%-CI]; p-value	0.52 [0.19, 1.39], 0.1837		0.71 [0.21, 2.45], 0.5882		0.59 [0.27, 1.28], 0.1784	
RD [95%-CI]; p-value	-0.07 [-0.18, 0.04], 0.2125		-0.02 [-0.11, 0.07], 0.6007		-0.05 [-0.12, 0.02], 0.2013	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.7.s7.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.3250		0.2829		0.2016	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	0/13 (0.0)	0/5 (0.0)	0/27 (0.0)	0/4 (0.0)	0/40 (0.0)	0/9 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	4/102 (3.9)	0/57 (0.0)	3/92 (3.3)	1/56 (1.8)	7/194 (3.6)	1/113 (0.9)
RR [95%-CI]; p-value	4.51 [0.24, 83.80], 0.3124		1.83 [0.19, 17.13], 0.5980		4.08 [0.51, 32.72], 0.1859	
OR [95%-CI]; p-value	4.65 [0.24, 89.62], 0.2637		1.85 [0.19, 18.27], 0.5915		4.19 [0.51, 34.52], 0.1486	
RD [95%-CI]; p-value	0.03 [-0.01, 0.08], 0.1805		0.01 [-0.04, 0.06], 0.5647		0.03 [-0.00, 0.06], 0.0893	

Abbreviations: CI: Confidence Interval; ER: Extended Release; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_7_m_pt_smq_dose_pp.sas using SAS 9.4

Table 12.4.4.1.6.s7.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Dose 30 ug vs 2.Dose 60 ug

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.8190		0.2721		0.5519	
1.Dose 30 ug	N1=13	N1=5	N1=27	N1=4	N1=40	N1=9
n/N1 (%)	1/13 (7.7)	1/5 (20.0)	4/27 (14.8)	1/4 (25.0)	5/40 (12.5)	2/9 (22.2)
RR [95%-CI]; p-value	0.38 [0.03, 5.04], 0.4667		0.59 [0.09, 4.06], 0.5939		0.56 [0.13, 2.45], 0.4436	
OR [95%-CI]; p-value	0.33 [0.02, 6.65], 0.4568		0.52 [0.04, 6.36], 0.6052		0.50 [0.08, 3.12], 0.4514	
RD [95%-CI]; p-value	-0.12 [-0.50, 0.26], 0.5248		-0.10 [-0.55, 0.34], 0.6537		-0.10 [-0.39, 0.19], 0.5116	
2.Dose 60 ug	N2=102	N2=57	N2=92	N2=56	N2=194	N2=113
n/N2 (%)	15/102 (14.7)	16/57 (28.1)	19/92 (20.7)	6/56 (10.7)	34/194 (17.5)	22/113 (19.5)
RR [95%-CI]; p-value	0.52 [0.28, 0.98], 0.0428		1.93 [0.82, 4.54], 0.1328		0.90 [0.56, 1.46], 0.6699	
OR [95%-CI]; p-value	0.44 [0.20, 0.98], 0.0414		2.17 [0.81, 5.81], 0.1176		0.88 [0.48, 1.59], 0.6707	
RD [95%-CI]; p-value	-0.13 [-0.27, 0.00], 0.0530		0.10 [-0.02, 0.22], 0.0925		-0.02 [-0.11, 0.07], 0.6739	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; OR: Odds Ratio; PP: Per-Protocol; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Only subjects who received actual treatment in Period 2 (after Week 12) are included in the analysis. Subjects who received ER-Calcifediol are classified into the dose group based on the treatment which they received (actual dose). Subjects who received placebo but met the uptitration criteria are classified into the dose group of 60 ug (expected dose); subjects who received placebo but didn't meet the uptitration criteria are classified into the dose group of 30 ug (expected dose).
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s7_dose_pp/T12_4_4_1_6_m_pt_adr_dose_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.1629		0.5568		0.0925	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	10/15 (66.7)	10/10 (100.0)	12/19 (63.2)	6/8 (75.0)	22/34 (64.7)	16/18 (88.9)
RR [95%-CI]; p-value	0.70 [0.48, 1.03], 0.0676		0.84 [0.50, 1.43], 0.5229		0.73 [0.54, 0.98], 0.0362	
OR [95%-CI]; p-value	0.10 [0.00, 2.08], 0.0843		0.57 [0.09, 3.64], 0.5511		0.23 [0.04, 1.17], 0.0614	
RD [95%-CI]; p-value	-0.29 [-0.56, -0.01], 0.0389		-0.12 [-0.49, 0.25], 0.5307		-0.24 [-0.46, -0.03], 0.0286	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	73/100 (73.0)	40/52 (76.9)	60/100 (60.0)	31/52 (59.6)	133/200 (66.5)	71/104 (68.3)
RR [95%-CI]; p-value	0.95 [0.78, 1.15], 0.5906		1.01 [0.76, 1.33], 0.9634		0.97 [0.83, 1.15], 0.7534	
OR [95%-CI]; p-value	0.81 [0.37, 1.77], 0.5993		1.02 [0.51, 2.01], 0.9634		0.92 [0.56, 1.53], 0.7554	
RD [95%-CI]; p-value	-0.04 [-0.18, 0.10], 0.5929		0.00 [-0.16, 0.17], 0.9634		-0.02 [-0.13, 0.09], 0.7543	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.1089		0.3430		0.0658	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	4/10 (40.0)	3/19 (15.8)	1/8 (12.5)	4/34 (11.8)	5/18 (27.8)
RR [95%-CI]; p-value	0.17 [0.02, 1.28], 0.0852		1.26 [0.15, 10.39], 0.8280		0.42 [0.13, 1.38], 0.1550	
OR [95%-CI]; p-value	0.11 [0.01, 1.17], 0.0412		1.31 [0.12, 14.93], 0.8261		0.35 [0.08, 1.50], 0.1465	
RD [95%-CI]; p-value	-0.33 [-0.66, -0.00], 0.0469		0.03 [-0.25, 0.31], 0.8190		-0.16 [-0.39, 0.07], 0.1790	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	12/100 (12.0)	6/52 (11.5)	10/100 (10.0)	1/52 (1.9)	22/200 (11.0)	7/104 (6.7)
RR [95%-CI]; p-value	1.04 [0.41, 2.61], 0.9335		5.20 [0.68, 39.52], 0.1111		1.63 [0.72, 3.70], 0.2386	
OR [95%-CI]; p-value	1.05 [0.37, 2.97], 0.9334		5.67 [0.71, 45.55], 0.0683		1.71 [0.71, 4.15], 0.2293	
RD [95%-CI]; p-value	0.00 [-0.10, 0.11], 0.9331		0.08 [0.01, 0.15], 0.0230		0.04 [-0.02, 0.11], 0.1966	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.6380		0.3455		0.5701	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	2/18 (11.1)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.10 [0.01, 2.03], 0.1352		0.53 [0.08, 3.45], 0.5061	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.08 [0.00, 2.00], 0.0631		0.50 [0.06, 3.88], 0.5008	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.22 [-0.53, 0.08], 0.1536		-0.05 [-0.22, 0.11], 0.5353	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	4/52 (7.7)	3/100 (3.0)	3/52 (5.8)	13/200 (6.5)	7/104 (6.7)
RR [95%-CI]; p-value	1.30 [0.43, 3.94], 0.6432		0.52 [0.11, 2.49], 0.4128		0.97 [0.40, 2.35], 0.9386	
OR [95%-CI]; p-value	1.33 [0.40, 4.48], 0.6407		0.51 [0.10, 2.60], 0.4055		0.96 [0.37, 2.49], 0.9386	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6278		-0.03 [-0.10, 0.04], 0.4488		-0.00 [-0.06, 0.06], 0.9389	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.2153		0.1787		0.8975	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	5/15 (33.3)	1/10 (10.0)	1/19 (5.3)	2/8 (25.0)	6/34 (17.6)	3/18 (16.7)
RR [95%-CI]; p-value	3.33 [0.45, 24.44], 0.2363		0.21 [0.02, 2.01], 0.1754		1.06 [0.30, 3.74], 0.9293	
OR [95%-CI]; p-value	4.50 [0.44, 46.17], 0.1808		0.17 [0.01, 2.18], 0.1362		1.07 [0.23, 4.90], 0.9292	
RD [95%-CI]; p-value	0.23 [-0.07, 0.54], 0.1305		-0.20 [-0.51, 0.12], 0.2215		0.01 [-0.20, 0.22], 0.9287	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	15/100 (15.0)	9/52 (17.3)	11/100 (11.0)	5/52 (9.6)	26/200 (13.0)	14/104 (13.5)
RR [95%-CI]; p-value	0.87 [0.41, 1.84], 0.7104		1.14 [0.42, 3.12], 0.7926		0.97 [0.53, 1.77], 0.9100	
OR [95%-CI]; p-value	0.84 [0.34, 2.08], 0.7113		1.16 [0.38, 3.54], 0.7919		0.96 [0.48, 1.93], 0.9101	
RD [95%-CI]; p-value	-0.02 [-0.15, 0.10], 0.7161		0.01 [-0.09, 0.11], 0.7880		-0.00 [-0.09, 0.08], 0.9105	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.7406		0.4914		0.3833	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	4/15 (26.7)	2/10 (20.0)	1/19 (5.3)	0/8 (0.0)	5/34 (14.7)	2/18 (11.1)
RR [95%-CI]; p-value	1.33 [0.30, 5.96], 0.7064		0.89 [0.03, 24.19], 0.9473		1.32 [0.28, 6.16], 0.7208	
OR [95%-CI]; p-value	1.45 [0.21, 9.98], 0.7022		0.89 [0.03, 29.30], 0.9473		1.38 [0.24, 7.94], 0.7179	
RD [95%-CI]; p-value	0.07 [-0.27, 0.40], 0.6956		-0.01 [-0.19, 0.18], 0.9484		0.04 [-0.15, 0.22], 0.7075	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	1/52 (1.9)	4/100 (4.0)	0/52 (0.0)	8/200 (4.0)	1/104 (1.0)
RR [95%-CI]; p-value	2.08 [0.24, 18.14], 0.5074		4.20 [0.23, 77.94], 0.3356		4.16 [0.53, 32.81], 0.1761	
OR [95%-CI]; p-value	2.13 [0.23, 19.52], 0.4958		4.33 [0.22, 83.56], 0.2907		4.29 [0.53, 34.79], 0.1381	
RD [95%-CI]; p-value	0.02 [-0.03, 0.07], 0.4472		0.03 [-0.02, 0.08], 0.1993		0.03 [-0.00, 0.06], 0.0712	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9126		NA		0.9899	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	1/52 (1.9)	0/100 (0.0)	0/52 (0.0)	1/200 (0.5)	1/104 (1.0)
RR [95%-CI]; p-value	0.52 [0.03, 8.15], 0.6413		NA		0.52 [0.03, 8.23], 0.6426	
OR [95%-CI]; p-value	0.52 [0.03, 8.41], 0.6356		NA		0.52 [0.03, 8.36], 0.6368	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.6675		NA		-0.00 [-0.03, 0.02], 0.6689	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.7122		NA		0.7822	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	0/100 (0.0)	1/52 (1.9)	0/100 (0.0)	0/52 (0.0)	0/200 (0.0)	1/104 (1.0)
RR [95%-CI]; p-value	0.26 [0.01, 7.58], 0.4328		NA		0.26 [0.01, 7.67], 0.4348	
OR [95%-CI]; p-value	0.26 [0.01, 7.73], 0.3978		NA		0.26 [0.01, 7.74], 0.3999	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.4825		NA		-0.01 [-0.03, 0.01], 0.4849	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.0482		0.9385		0.1440	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	6/15 (40.0)	9/10 (90.0)	12/19 (63.2)	5/8 (62.5)	18/34 (52.9)	14/18 (77.8)
RR [95%-CI]; p-value	0.44 [0.23, 0.85], 0.0150		1.01 [0.53, 1.91], 0.9743		0.68 [0.46, 1.02], 0.0606	
OR [95%-CI]; p-value	0.07 [0.01, 0.75], 0.0124		1.03 [0.19, 5.68], 0.9742		0.32 [0.09, 1.18], 0.0799	
RD [95%-CI]; p-value	-0.50 [-0.81, -0.19], 0.0016		0.01 [-0.39, 0.41], 0.9743		-0.25 [-0.50, 0.01], 0.0563	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	62/100 (62.0)	36/52 (69.2)	48/100 (48.0)	24/52 (46.2)	110/200 (55.0)	60/104 (57.7)
RR [95%-CI]; p-value	0.90 [0.71, 1.14], 0.3625		1.04 [0.73, 1.49], 0.8297		0.95 [0.78, 1.17], 0.6507	
OR [95%-CI]; p-value	0.73 [0.36, 1.48], 0.3769		1.08 [0.55, 2.11], 0.8288		0.90 [0.56, 1.45], 0.6538	
RD [95%-CI]; p-value	-0.07 [-0.23, 0.09], 0.3680		0.02 [-0.15, 0.19], 0.8286		-0.03 [-0.14, 0.09], 0.6529	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.4263		0.1177		0.5989	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	7/15 (46.7)	4/10 (40.0)	5/19 (26.3)	4/8 (50.0)	12/34 (35.3)	8/18 (44.4)
RR [95%-CI]; p-value	1.17 [0.46, 2.96], 0.7458		0.53 [0.19, 1.46], 0.2187		0.79 [0.40, 1.58], 0.5116	
OR [95%-CI]; p-value	1.31 [0.26, 6.64], 0.7422		0.36 [0.06, 2.00], 0.2332		0.68 [0.21, 2.19], 0.5188	
RD [95%-CI]; p-value	0.07 [-0.33, 0.46], 0.7407		-0.24 [-0.64, 0.16], 0.2447		-0.09 [-0.37, 0.19], 0.5221	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	31/100 (31.0)	21/52 (40.4)	31/100 (31.0)	12/52 (23.1)	62/200 (31.0)	33/104 (31.7)
RR [95%-CI]; p-value	0.77 [0.49, 1.19], 0.2399		1.34 [0.76, 2.39], 0.3152		0.98 [0.69, 1.39], 0.8961	
OR [95%-CI]; p-value	0.66 [0.33, 1.33], 0.2473		1.50 [0.69, 3.24], 0.3035		0.97 [0.58, 1.61], 0.8962	
RD [95%-CI]; p-value	-0.09 [-0.26, 0.07], 0.2540		0.08 [-0.07, 0.23], 0.2877		-0.01 [-0.12, 0.10], 0.8964	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s8.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.6380		0.3455		0.5701	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	2/18 (11.1)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.10 [0.01, 2.03], 0.1352		0.53 [0.08, 3.45], 0.5061	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.08 [0.00, 2.00], 0.0631		0.50 [0.06, 3.88], 0.5008	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.22 [-0.53, 0.08], 0.1536		-0.05 [-0.22, 0.11], 0.5353	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	4/52 (7.7)	3/100 (3.0)	3/52 (5.8)	13/200 (6.5)	7/104 (6.7)
RR [95%-CI]; p-value	1.30 [0.43, 3.94], 0.6432		0.52 [0.11, 2.49], 0.4128		0.97 [0.40, 2.35], 0.9386	
OR [95%-CI]; p-value	1.33 [0.40, 4.48], 0.6407		0.51 [0.10, 2.60], 0.4055		0.96 [0.37, 2.49], 0.9386	
RD [95%-CI]; p-value	0.02 [-0.07, 0.12], 0.6278		-0.03 [-0.10, 0.04], 0.4488		-0.00 [-0.06, 0.06], 0.9389	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_3_1_m_sf_ttl_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.8734		0.7653		0.6599	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	3/10 (30.0)	1/19 (5.3)	0/8 (0.0)	3/34 (8.8)	3/18 (16.7)
RR [95%-CI]; p-value	0.44 [0.09, 2.20], 0.3206		0.89 [0.03, 24.19], 0.9473		0.53 [0.12, 2.36], 0.4044	
OR [95%-CI]; p-value	0.36 [0.05, 2.68], 0.3074		0.89 [0.03, 29.30], 0.9473		0.48 [0.09, 2.69], 0.3997	
RD [95%-CI]; p-value	-0.17 [-0.50, 0.17], 0.3252		-0.01 [-0.19, 0.18], 0.9484		-0.08 [-0.28, 0.12], 0.4347	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	6/100 (6.0)	2/52 (3.8)	12/200 (6.0)	8/104 (7.7)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		1.56 [0.33, 7.46], 0.5775		0.78 [0.33, 1.85], 0.5724	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		1.60 [0.31, 8.20], 0.5726		0.77 [0.30, 1.94], 0.5723	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.02 [-0.05, 0.09], 0.5464		-0.02 [-0.08, 0.04], 0.5859	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6511		0.5234		0.7846	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	3/10 (30.0)	6/19 (31.6)	2/8 (25.0)	8/34 (23.5)	5/18 (27.8)
RR [95%-CI]; p-value	0.44 [0.09, 2.20], 0.3206		1.26 [0.32, 4.97], 0.7383		0.85 [0.32, 2.21], 0.7348	
OR [95%-CI]; p-value	0.36 [0.05, 2.68], 0.3074		1.38 [0.21, 8.98], 0.7325		0.80 [0.22, 2.94], 0.7364	
RD [95%-CI]; p-value	-0.17 [-0.50, 0.17], 0.3252		0.07 [-0.30, 0.43], 0.7244		-0.04 [-0.29, 0.21], 0.7404	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	19/100 (19.0)	15/52 (28.8)	17/100 (17.0)	4/52 (7.7)	36/200 (18.0)	19/104 (18.3)
RR [95%-CI]; p-value	0.66 [0.37, 1.19], 0.1641		2.21 [0.78, 6.23], 0.1337		0.99 [0.60, 1.63], 0.9538	
OR [95%-CI]; p-value	0.58 [0.27, 1.26], 0.1670		2.46 [0.78, 7.73], 0.1146		0.98 [0.53, 1.82], 0.9539	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.05], 0.1837		0.09 [-0.01, 0.20], 0.0773		-0.00 [-0.09, 0.09], 0.9540	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.3993		0.0977		0.4155	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	1/10 (10.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	1.33 [0.14, 12.82], 0.8033		0.10 [0.01, 2.03], 0.1352		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	1.38 [0.11, 17.67], 0.8016		0.08 [0.00, 2.00], 0.0631		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	0.03 [-0.22, 0.29], 0.7965		-0.22 [-0.53, 0.08], 0.1536		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	13/100 (13.0)	14/52 (26.9)	14/100 (14.0)	5/52 (9.6)	27/200 (13.5)	19/104 (18.3)
RR [95%-CI]; p-value	0.48 [0.25, 0.95], 0.0349		1.46 [0.55, 3.82], 0.4452		0.74 [0.43, 1.26], 0.2695	
OR [95%-CI]; p-value	0.41 [0.17, 0.94], 0.0331		1.53 [0.52, 4.51], 0.4381		0.70 [0.37, 1.33], 0.2710	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0470		0.04 [-0.06, 0.15], 0.4135		-0.05 [-0.14, 0.04], 0.2886	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.8339		0.6020		0.7063	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	5/15 (33.3)	3/10 (30.0)	4/19 (21.1)	1/8 (12.5)	9/34 (26.5)	4/18 (22.2)
RR [95%-CI]; p-value	1.11 [0.34, 3.64], 0.8619		1.68 [0.22, 12.82], 0.6147		1.19 [0.43, 3.34], 0.7392	
OR [95%-CI]; p-value	1.17 [0.21, 6.56], 0.8611		1.87 [0.17, 19.93], 0.6014		1.26 [0.33, 4.85], 0.7364	
RD [95%-CI]; p-value	0.03 [-0.34, 0.40], 0.8602		0.09 [-0.21, 0.38], 0.5679		0.04 [-0.20, 0.29], 0.7315	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	26/100 (26.0)	14/52 (26.9)	24/100 (24.0)	13/52 (25.0)	50/200 (25.0)	27/104 (26.0)
RR [95%-CI]; p-value	0.97 [0.55, 1.68], 0.9022		0.96 [0.53, 1.72], 0.8914		0.96 [0.64, 1.44], 0.8546	
OR [95%-CI]; p-value	0.95 [0.45, 2.04], 0.9024		0.95 [0.44, 2.06], 0.8916		0.95 [0.55, 1.64], 0.8549	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9028		-0.01 [-0.15, 0.13], 0.8921		-0.01 [-0.11, 0.09], 0.8554	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.1739		0.0566		0.8560	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	4/15 (26.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	6/34 (17.6)	4/18 (22.2)
RR [95%-CI]; p-value	2.67 [0.35, 20.51], 0.3460		0.28 [0.06, 1.37], 0.1167		0.79 [0.26, 2.46], 0.6890	
OR [95%-CI]; p-value	3.27 [0.31, 34.72], 0.3074		0.20 [0.03, 1.52], 0.0994		0.75 [0.18, 3.10], 0.6904	
RD [95%-CI]; p-value	0.17 [-0.12, 0.46], 0.2616		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.28, 0.19], 0.6977	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	9/52 (17.3)	9/100 (9.0)	2/52 (3.8)	19/200 (9.5)	11/104 (10.6)
RR [95%-CI]; p-value	0.58 [0.25, 1.33], 0.1983		2.34 [0.52, 10.44], 0.2651		0.90 [0.44, 1.82], 0.7649	
OR [95%-CI]; p-value	0.53 [0.20, 1.40], 0.1962		2.47 [0.51, 11.89], 0.2446		0.89 [0.41, 1.94], 0.7652	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2266		0.05 [-0.03, 0.13], 0.1877		-0.01 [-0.08, 0.06], 0.7686	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5539		0.7262		0.9448	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	2/10 (20.0)	3/19 (15.8)	1/8 (12.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	0.33 [0.03, 3.20], 0.3414		1.26 [0.15, 10.39], 0.8280		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	0.29 [0.02, 3.67], 0.3149		1.31 [0.12, 14.93], 0.8261		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	-0.13 [-0.41, 0.14], 0.3476		0.03 [-0.25, 0.31], 0.8190		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	22/100 (22.0)	17/52 (32.7)	18/100 (18.0)	11/52 (21.2)	40/200 (20.0)	28/104 (26.9)
RR [95%-CI]; p-value	0.67 [0.39, 1.15], 0.1482		0.85 [0.43, 1.66], 0.6373		0.74 [0.49, 1.13], 0.1662	
OR [95%-CI]; p-value	0.58 [0.27, 1.23], 0.1522		0.82 [0.35, 1.89], 0.6387		0.68 [0.39, 1.18], 0.1694	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1656		-0.03 [-0.17, 0.10], 0.6449		-0.07 [-0.17, 0.03], 0.1821	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
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Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2827		0.1594		0.0868	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	5/10 (50.0)	3/19 (15.8)	4/8 (50.0)	5/34 (14.7)	9/18 (50.0)
RR [95%-CI]; p-value	0.27 [0.06, 1.12], 0.0703		0.32 [0.09, 1.10], 0.0703		0.29 [0.12, 0.75], 0.0101	
OR [95%-CI]; p-value	0.15 [0.02, 1.07], 0.0455		0.19 [0.03, 1.20], 0.0640		0.17 [0.05, 0.65], 0.0063	
RD [95%-CI]; p-value	-0.37 [-0.72, -0.01], 0.0426		-0.34 [-0.73, 0.04], 0.0802		-0.35 [-0.61, -0.09], 0.0078	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	18/100 (18.0)	15/52 (28.8)	17/100 (17.0)	10/52 (19.2)	35/200 (17.5)	25/104 (24.0)
RR [95%-CI]; p-value	0.62 [0.34, 1.13], 0.1220		0.88 [0.44, 1.79], 0.7320		0.73 [0.46, 1.15], 0.1717	
OR [95%-CI]; p-value	0.54 [0.25, 1.19], 0.1239		0.86 [0.36, 2.04], 0.7328		0.67 [0.38, 1.20], 0.1742	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.04], 0.1408		-0.02 [-0.15, 0.11], 0.7366		-0.07 [-0.16, 0.03], 0.1890	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8607		0.0979		0.3845	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.05, 9.47], 0.7646		0.28 [0.06, 1.37], 0.1167		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.64 [0.04, 11.63], 0.7634		0.20 [0.03, 1.52], 0.0994		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.19], 0.7713		-0.27 [-0.63, 0.09], 0.1450		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	10/52 (19.2)	11/100 (11.0)	4/52 (7.7)	21/200 (10.5)	14/104 (13.5)
RR [95%-CI]; p-value	0.52 [0.23, 1.17], 0.1136		1.43 [0.48, 4.27], 0.5217		0.78 [0.41, 1.47], 0.4420	
OR [95%-CI]; p-value	0.47 [0.18, 1.21], 0.1102		1.48 [0.45, 4.91], 0.5165		0.75 [0.37, 1.55], 0.4428	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1387		0.03 [-0.06, 0.13], 0.4945		-0.03 [-0.11, 0.05], 0.4577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.3106		0.9364		0.3018	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	0/10 (0.0)	1/19 (5.3)	0/8 (0.0)	2/34 (5.9)	0/18 (0.0)
RR [95%-CI]; p-value	1.40 [0.05, 38.03], 0.8417		0.89 [0.03, 24.19], 0.9473		2.18 [0.10, 45.81], 0.6169	
OR [95%-CI]; p-value	1.43 [0.04, 46.86], 0.8406		0.89 [0.03, 29.30], 0.9473		2.25 [0.10, 52.63], 0.6053	
RD [95%-CI]; p-value	0.02 [-0.16, 0.20], 0.8360		-0.01 [-0.19, 0.18], 0.9484		0.03 [-0.08, 0.14], 0.5648	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	3/100 (3.0)	7/52 (13.5)	4/100 (4.0)	2/52 (3.8)	7/200 (3.5)	9/104 (8.7)
RR [95%-CI]; p-value	0.22 [0.06, 0.83], 0.0247		1.04 [0.20, 5.49], 0.9632		0.40 [0.16, 1.06], 0.0643	
OR [95%-CI]; p-value	0.20 [0.05, 0.80], 0.0136		1.04 [0.18, 5.88], 0.9631		0.38 [0.14, 1.06], 0.0562	
RD [95%-CI]; p-value	-0.10 [-0.20, -0.01], 0.0376		0.00 [-0.06, 0.07], 0.9629		-0.05 [-0.11, 0.01], 0.0908	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1844		0.5350		0.2212	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	3/10 (30.0)	4/19 (21.1)	2/8 (25.0)	5/34 (14.7)	5/18 (27.8)
RR [95%-CI]; p-value	0.22 [0.03, 1.85], 0.1638		0.84 [0.19, 3.71], 0.8203		0.53 [0.18, 1.59], 0.2572	
OR [95%-CI]; p-value	0.17 [0.01, 1.91], 0.1190		0.80 [0.11, 5.59], 0.8218		0.45 [0.11, 1.82], 0.2552	
RD [95%-CI]; p-value	-0.23 [-0.54, 0.08], 0.1412		-0.04 [-0.39, 0.31], 0.8258		-0.13 [-0.37, 0.11], 0.2832	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	14/100 (14.0)	7/52 (13.5)	9/100 (9.0)	3/52 (5.8)	23/200 (11.5)	10/104 (9.6)
RR [95%-CI]; p-value	1.04 [0.45, 2.42], 0.9274		1.56 [0.44, 5.52], 0.4901		1.20 [0.59, 2.42], 0.6181	
OR [95%-CI]; p-value	1.05 [0.39, 2.78], 0.9273		1.62 [0.42, 6.24], 0.4834		1.22 [0.56, 2.67], 0.6163	
RD [95%-CI]; p-value	0.01 [-0.11, 0.12], 0.9269		0.03 [-0.05, 0.12], 0.4543		0.02 [-0.05, 0.09], 0.6073	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4712		0.0323		0.0469	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	2/10 (20.0)	0/19 (0.0)	3/8 (37.5)	0/34 (0.0)	5/18 (27.8)
RR [95%-CI]; p-value	0.16 [0.01, 3.22], 0.2325		0.07 [0.00, 1.22], 0.0678		0.05 [0.00, 0.90], 0.0423	
OR [95%-CI]; p-value	0.13 [0.01, 3.32], 0.1643		0.04 [0.00, 1.03], 0.0125		0.04 [0.00, 0.75], 0.0031	
RD [95%-CI]; p-value	-0.17 [-0.43, 0.10], 0.2114		-0.35 [-0.69, -0.01], 0.0457		-0.26 [-0.47, -0.05], 0.0143	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	12/100 (12.0)	3/52 (5.8)	18/200 (9.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		2.08 [0.61, 7.05], 0.2394		1.04 [0.48, 2.23], 0.9199	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		2.23 [0.60, 8.28], 0.2217		1.04 [0.45, 2.41], 0.9198	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.06 [-0.03, 0.15], 0.1741		0.00 [-0.06, 0.07], 0.9194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.1.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.5594		0.9844		0.4465	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	1/10 (10.0)	1/19 (5.3)	1/8 (12.5)	1/34 (2.9)	2/18 (11.1)
RR [95%-CI]; p-value	0.32 [0.01, 8.75], 0.5016		0.42 [0.03, 5.93], 0.5217		0.26 [0.03, 2.72], 0.2638	
OR [95%-CI]; p-value	0.30 [0.01, 9.87], 0.4778		0.39 [0.02, 7.11], 0.5121		0.24 [0.02, 2.88], 0.2293	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.14], 0.5186		-0.07 [-0.32, 0.18], 0.5708		-0.08 [-0.24, 0.07], 0.3043	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	12/100 (12.0)	7/52 (13.5)	5/100 (5.0)	6/52 (11.5)	17/200 (8.5)	13/104 (12.5)
RR [95%-CI]; p-value	0.89 [0.37, 2.13], 0.7957		0.43 [0.14, 1.35], 0.1500		0.68 [0.34, 1.35], 0.2678	
OR [95%-CI]; p-value	0.88 [0.32, 2.38], 0.7960		0.40 [0.12, 1.39], 0.1399		0.65 [0.30, 1.40], 0.2673	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.10], 0.7991		-0.07 [-0.16, 0.03], 0.1854		-0.04 [-0.11, 0.03], 0.2919	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_1_m_soc_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.6285		0.6892		0.7842	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	3/10 (30.0)	2/19 (10.5)	0/8 (0.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	0.11 [0.01, 1.93], 0.1300		1.79 [0.09, 35.64], 0.7030		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	0.08 [0.00, 1.77], 0.0551		1.88 [0.08, 46.68], 0.6954		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	-0.27 [-0.57, 0.03], 0.0776		0.05 [-0.16, 0.26], 0.6646		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	9/52 (17.3)	4/100 (4.0)	0/52 (0.0)	8/200 (4.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.23 [0.07, 0.71], 0.0110		4.20 [0.23, 77.94], 0.3356		0.46 [0.18, 1.16], 0.1011	
OR [95%-CI]; p-value	0.20 [0.06, 0.68], 0.0054		4.33 [0.22, 83.56], 0.2907		0.44 [0.16, 1.18], 0.0939	
RD [95%-CI]; p-value	-0.13 [-0.24, -0.02], 0.0175		0.03 [-0.02, 0.08], 0.1993		-0.05 [-0.11, 0.01], 0.1315	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_3_m_pt_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.6398		0.4752		0.5767	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	2/19 (10.5)	1/8 (12.5)	2/34 (5.9)	1/18 (5.6)
RR [95%-CI]; p-value	0.68 [0.01, 31.54], 0.8425		0.84 [0.09, 8.02], 0.8812		1.06 [0.10, 10.90], 0.9617	
OR [95%-CI]; p-value	0.67 [0.01, 36.43], 0.8416		0.82 [0.06, 10.62], 0.8815		1.06 [0.09, 12.58], 0.9616	
RD [95%-CI]; p-value	-0.02 [-0.17, 0.14], 0.8469		-0.02 [-0.29, 0.25], 0.8850		0.00 [-0.13, 0.14], 0.9613	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	8/52 (15.4)	5/100 (5.0)	1/52 (1.9)	9/200 (4.5)	9/104 (8.7)
RR [95%-CI]; p-value	0.26 [0.08, 0.82], 0.0220		2.60 [0.31, 21.68], 0.3772		0.52 [0.21, 1.27], 0.1512	
OR [95%-CI]; p-value	0.23 [0.07, 0.80], 0.0135		2.68 [0.31, 23.60], 0.3554		0.50 [0.19, 1.29], 0.1454	
RD [95%-CI]; p-value	-0.11 [-0.22, -0.01], 0.0341		0.03 [-0.03, 0.09], 0.2877		-0.04 [-0.10, 0.02], 0.1834	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_3_m_pt_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.3.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.4196		0.9112		0.5785	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	1/10 (10.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	1/18 (5.6)
RR [95%-CI]; p-value	0.32 [0.01, 8.75], 0.5016		0.44 [0.01, 20.20], 0.6714		0.26 [0.01, 7.41], 0.4313	
OR [95%-CI]; p-value	0.30 [0.01, 9.87], 0.4778		0.42 [0.01, 23.13], 0.6635		0.25 [0.01, 7.83], 0.3966	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.14], 0.5186		-0.03 [-0.21, 0.14], 0.7070		-0.04 [-0.15, 0.07], 0.4767	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	8/100 (8.0)	3/52 (5.8)	4/100 (4.0)	6/52 (11.5)	12/200 (6.0)	9/104 (8.7)
RR [95%-CI]; p-value	1.39 [0.38, 5.01], 0.6177		0.35 [0.10, 1.17], 0.0888		0.69 [0.30, 1.59], 0.3878	
OR [95%-CI]; p-value	1.42 [0.36, 5.60], 0.6146		0.32 [0.09, 1.19], 0.0753		0.67 [0.27, 1.66], 0.3867	
RD [95%-CI]; p-value	0.02 [-0.06, 0.11], 0.5971		-0.08 [-0.17, 0.02], 0.1197		-0.03 [-0.09, 0.04], 0.4110	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_3_m_pt_ae10pct_vitd_pp.sas using SAS 9.4

Table 12.4.8.1.1.s8.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6515		0.9153		0.5825	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	1/34 (2.9)	0/18 (0.0)
RR [95%-CI]; p-value	1.40 [0.05, 38.03], 0.8417		0.44 [0.01, 20.20], 0.6714		1.09 [0.04, 30.93], 0.9605	
OR [95%-CI]; p-value	1.43 [0.04, 46.86], 0.8406		0.42 [0.01, 23.13], 0.6635		1.09 [0.03, 34.12], 0.9605	
RD [95%-CI]; p-value	0.02 [-0.16, 0.20], 0.8360		-0.03 [-0.21, 0.14], 0.7070		0.00 [-0.09, 0.10], 0.9600	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	1/52 (1.9)	2/100 (2.0)	3/52 (5.8)	3/200 (1.5)	4/104 (3.8)
RR [95%-CI]; p-value	0.52 [0.03, 8.15], 0.6413		0.35 [0.06, 2.01], 0.2374		0.39 [0.09, 1.71], 0.2118	
OR [95%-CI]; p-value	0.52 [0.03, 8.41], 0.6356		0.33 [0.05, 2.06], 0.2164		0.38 [0.08, 1.73], 0.1957	
RD [95%-CI]; p-value	-0.01 [-0.05, 0.03], 0.6675		-0.04 [-0.11, 0.03], 0.2847		-0.02 [-0.06, 0.02], 0.2576	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_8_1_1_m_soc_sae5pct_vitd_pp.sas using SAS 9.4

Table 12.4.8.1.2.s8.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_8_1_2_m_pt_sae5pct_vitd_pp.sas using SAS 9.4

Table 12.4.5.1.1.s8.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_5_1_1_m_soc_aeg35pct_vitd_pp.sas using SAS 9.4

Table 12.4.5.1.2.s8.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_5_1_2_m_pt_aeg35pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.6511		0.5234		0.7846	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	3/10 (30.0)	6/19 (31.6)	2/8 (25.0)	8/34 (23.5)	5/18 (27.8)
RR [95%-CI]; p-value	0.44 [0.09, 2.20], 0.3206		1.26 [0.32, 4.97], 0.7383		0.85 [0.32, 2.21], 0.7348	
OR [95%-CI]; p-value	0.36 [0.05, 2.68], 0.3074		1.38 [0.21, 8.98], 0.7325		0.80 [0.22, 2.94], 0.7364	
RD [95%-CI]; p-value	-0.17 [-0.50, 0.17], 0.3252		0.07 [-0.30, 0.43], 0.7244		-0.04 [-0.29, 0.21], 0.7404	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	19/100 (19.0)	15/52 (28.8)	17/100 (17.0)	4/52 (7.7)	36/200 (18.0)	19/104 (18.3)
RR [95%-CI]; p-value	0.66 [0.37, 1.19], 0.1641		2.21 [0.78, 6.23], 0.1337		0.99 [0.60, 1.63], 0.9538	
OR [95%-CI]; p-value	0.58 [0.27, 1.26], 0.1670		2.46 [0.78, 7.73], 0.1146		0.98 [0.53, 1.82], 0.9539	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.05], 0.1837		0.09 [-0.01, 0.20], 0.0773		-0.00 [-0.09, 0.09], 0.9540	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.3993		0.0977		0.4155	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	1/10 (10.0)	0/19 (0.0)	2/8 (25.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	1.33 [0.14, 12.82], 0.8033		0.10 [0.01, 2.03], 0.1352		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	1.38 [0.11, 17.67], 0.8016		0.08 [0.00, 2.00], 0.0631		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	0.03 [-0.22, 0.29], 0.7965		-0.22 [-0.53, 0.08], 0.1536		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	13/100 (13.0)	14/52 (26.9)	14/100 (14.0)	5/52 (9.6)	27/200 (13.5)	19/104 (18.3)
RR [95%-CI]; p-value	0.48 [0.25, 0.95], 0.0349		1.46 [0.55, 3.82], 0.4452		0.74 [0.43, 1.26], 0.2695	
OR [95%-CI]; p-value	0.41 [0.17, 0.94], 0.0331		1.53 [0.52, 4.51], 0.4381		0.70 [0.37, 1.33], 0.2710	
RD [95%-CI]; p-value	-0.14 [-0.28, -0.00], 0.0470		0.04 [-0.06, 0.15], 0.4135		-0.05 [-0.14, 0.04], 0.2886	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.8339		0.6020		0.7063	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	5/15 (33.3)	3/10 (30.0)	4/19 (21.1)	1/8 (12.5)	9/34 (26.5)	4/18 (22.2)
RR [95%-CI]; p-value	1.11 [0.34, 3.64], 0.8619		1.68 [0.22, 12.82], 0.6147		1.19 [0.43, 3.34], 0.7392	
OR [95%-CI]; p-value	1.17 [0.21, 6.56], 0.8611		1.87 [0.17, 19.93], 0.6014		1.26 [0.33, 4.85], 0.7364	
RD [95%-CI]; p-value	0.03 [-0.34, 0.40], 0.8602		0.09 [-0.21, 0.38], 0.5679		0.04 [-0.20, 0.29], 0.7315	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	26/100 (26.0)	14/52 (26.9)	24/100 (24.0)	13/52 (25.0)	50/200 (25.0)	27/104 (26.0)
RR [95%-CI]; p-value	0.97 [0.55, 1.68], 0.9022		0.96 [0.53, 1.72], 0.8914		0.96 [0.64, 1.44], 0.8546	
OR [95%-CI]; p-value	0.95 [0.45, 2.04], 0.9024		0.95 [0.44, 2.06], 0.8916		0.95 [0.55, 1.64], 0.8549	
RD [95%-CI]; p-value	-0.01 [-0.16, 0.14], 0.9028		-0.01 [-0.15, 0.13], 0.8921		-0.01 [-0.11, 0.09], 0.8554	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.9193		0.9365		0.6783	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	1/10 (10.0)	2/19 (10.5)	0/8 (0.0)	4/34 (11.8)	1/18 (5.6)
RR [95%-CI]; p-value	1.33 [0.14, 12.82], 0.8033		1.79 [0.09, 35.64], 0.7030		2.12 [0.26, 17.56], 0.4870	
OR [95%-CI]; p-value	1.38 [0.11, 17.67], 0.8016		1.88 [0.08, 46.68], 0.6954		2.27 [0.23, 21.95], 0.4699	
RD [95%-CI]; p-value	0.03 [-0.22, 0.29], 0.7965		0.05 [-0.16, 0.26], 0.6646		0.06 [-0.09, 0.21], 0.4215	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	9/100 (9.0)	4/52 (7.7)	6/100 (6.0)	2/52 (3.8)	15/200 (7.5)	6/104 (5.8)
RR [95%-CI]; p-value	1.17 [0.38, 3.62], 0.7852		1.56 [0.33, 7.46], 0.5775		1.30 [0.52, 3.25], 0.5748	
OR [95%-CI]; p-value	1.19 [0.35, 4.05], 0.7845		1.60 [0.31, 8.20], 0.5726		1.32 [0.50, 3.52], 0.5724	
RD [95%-CI]; p-value	0.01 [-0.08, 0.10], 0.7796		0.02 [-0.05, 0.09], 0.5464		0.02 [-0.04, 0.08], 0.5573	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.1739		0.0566		0.8560	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	4/15 (26.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	6/34 (17.6)	4/18 (22.2)
RR [95%-CI]; p-value	2.67 [0.35, 20.51], 0.3460		0.28 [0.06, 1.37], 0.1167		0.79 [0.26, 2.46], 0.6890	
OR [95%-CI]; p-value	3.27 [0.31, 34.72], 0.3074		0.20 [0.03, 1.52], 0.0994		0.75 [0.18, 3.10], 0.6904	
RD [95%-CI]; p-value	0.17 [-0.12, 0.46], 0.2616		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.28, 0.19], 0.6977	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	9/52 (17.3)	9/100 (9.0)	2/52 (3.8)	19/200 (9.5)	11/104 (10.6)
RR [95%-CI]; p-value	0.58 [0.25, 1.33], 0.1983		2.34 [0.52, 10.44], 0.2651		0.90 [0.44, 1.82], 0.7649	
OR [95%-CI]; p-value	0.53 [0.20, 1.40], 0.1962		2.47 [0.51, 11.89], 0.2446		0.89 [0.41, 1.94], 0.7652	
RD [95%-CI]; p-value	-0.07 [-0.19, 0.05], 0.2266		0.05 [-0.03, 0.13], 0.1877		-0.01 [-0.08, 0.06], 0.7686	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.5539		0.7262		0.9448	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	2/10 (20.0)	3/19 (15.8)	1/8 (12.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	0.33 [0.03, 3.20], 0.3414		1.26 [0.15, 10.39], 0.8280		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	0.29 [0.02, 3.67], 0.3149		1.31 [0.12, 14.93], 0.8261		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	-0.13 [-0.41, 0.14], 0.3476		0.03 [-0.25, 0.31], 0.8190		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	22/100 (22.0)	17/52 (32.7)	18/100 (18.0)	11/52 (21.2)	40/200 (20.0)	28/104 (26.9)
RR [95%-CI]; p-value	0.67 [0.39, 1.15], 0.1482		0.85 [0.43, 1.66], 0.6373		0.74 [0.49, 1.13], 0.1662	
OR [95%-CI]; p-value	0.58 [0.27, 1.23], 0.1522		0.82 [0.35, 1.89], 0.6387		0.68 [0.39, 1.18], 0.1694	
RD [95%-CI]; p-value	-0.11 [-0.26, 0.04], 0.1656		-0.03 [-0.17, 0.10], 0.6449		-0.07 [-0.17, 0.03], 0.1821	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.2827		0.1594		0.0868	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	5/10 (50.0)	3/19 (15.8)	4/8 (50.0)	5/34 (14.7)	9/18 (50.0)
RR [95%-CI]; p-value	0.27 [0.06, 1.12], 0.0703		0.32 [0.09, 1.10], 0.0703		0.29 [0.12, 0.75], 0.0101	
OR [95%-CI]; p-value	0.15 [0.02, 1.07], 0.0455		0.19 [0.03, 1.20], 0.0640		0.17 [0.05, 0.65], 0.0063	
RD [95%-CI]; p-value	-0.37 [-0.72, -0.01], 0.0426		-0.34 [-0.73, 0.04], 0.0802		-0.35 [-0.61, -0.09], 0.0078	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	18/100 (18.0)	15/52 (28.8)	17/100 (17.0)	10/52 (19.2)	35/200 (17.5)	25/104 (24.0)
RR [95%-CI]; p-value	0.62 [0.34, 1.13], 0.1220		0.88 [0.44, 1.79], 0.7320		0.73 [0.46, 1.15], 0.1717	
OR [95%-CI]; p-value	0.54 [0.25, 1.19], 0.1239		0.86 [0.36, 2.04], 0.7328		0.67 [0.38, 1.20], 0.1742	
RD [95%-CI]; p-value	-0.11 [-0.25, 0.04], 0.1408		-0.02 [-0.15, 0.11], 0.7366		-0.07 [-0.16, 0.03], 0.1890	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8607		0.0979		0.3845	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	1/10 (10.0)	2/19 (10.5)	3/8 (37.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.05, 9.47], 0.7646		0.28 [0.06, 1.37], 0.1167		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.64 [0.04, 11.63], 0.7634		0.20 [0.03, 1.52], 0.0994		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.03 [-0.26, 0.19], 0.7713		-0.27 [-0.63, 0.09], 0.1450		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	10/100 (10.0)	10/52 (19.2)	11/100 (11.0)	4/52 (7.7)	21/200 (10.5)	14/104 (13.5)
RR [95%-CI]; p-value	0.52 [0.23, 1.17], 0.1136		1.43 [0.48, 4.27], 0.5217		0.78 [0.41, 1.47], 0.4420	
OR [95%-CI]; p-value	0.47 [0.18, 1.21], 0.1102		1.48 [0.45, 4.91], 0.5165		0.75 [0.37, 1.55], 0.4428	
RD [95%-CI]; p-value	-0.09 [-0.21, 0.03], 0.1387		0.03 [-0.06, 0.13], 0.4945		-0.03 [-0.11, 0.05], 0.4577	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.1844		0.5350		0.2212	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	3/10 (30.0)	4/19 (21.1)	2/8 (25.0)	5/34 (14.7)	5/18 (27.8)
RR [95%-CI]; p-value	0.22 [0.03, 1.85], 0.1638		0.84 [0.19, 3.71], 0.8203		0.53 [0.18, 1.59], 0.2572	
OR [95%-CI]; p-value	0.17 [0.01, 1.91], 0.1190		0.80 [0.11, 5.59], 0.8218		0.45 [0.11, 1.82], 0.2552	
RD [95%-CI]; p-value	-0.23 [-0.54, 0.08], 0.1412		-0.04 [-0.39, 0.31], 0.8258		-0.13 [-0.37, 0.11], 0.2832	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	14/100 (14.0)	7/52 (13.5)	9/100 (9.0)	3/52 (5.8)	23/200 (11.5)	10/104 (9.6)
RR [95%-CI]; p-value	1.04 [0.45, 2.42], 0.9274		1.56 [0.44, 5.52], 0.4901		1.20 [0.59, 2.42], 0.6181	
OR [95%-CI]; p-value	1.05 [0.39, 2.78], 0.9273		1.62 [0.42, 6.24], 0.4834		1.22 [0.56, 2.67], 0.6163	
RD [95%-CI]; p-value	0.01 [-0.11, 0.12], 0.9269		0.03 [-0.05, 0.12], 0.4543		0.02 [-0.05, 0.09], 0.6073	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.4712		0.0323		0.0469	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	2/10 (20.0)	0/19 (0.0)	3/8 (37.5)	0/34 (0.0)	5/18 (27.8)
RR [95%-CI]; p-value	0.16 [0.01, 3.22], 0.2325		0.07 [0.00, 1.22], 0.0678		0.05 [0.00, 0.90], 0.0423	
OR [95%-CI]; p-value	0.13 [0.01, 3.32], 0.1643		0.04 [0.00, 1.03], 0.0125		0.04 [0.00, 0.75], 0.0031	
RD [95%-CI]; p-value	-0.17 [-0.43, 0.10], 0.2114		-0.35 [-0.69, -0.01], 0.0457		-0.26 [-0.47, -0.05], 0.0143	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	12/100 (12.0)	3/52 (5.8)	18/200 (9.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		2.08 [0.61, 7.05], 0.2394		1.04 [0.48, 2.23], 0.9199	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		2.23 [0.60, 8.28], 0.2217		1.04 [0.45, 2.41], 0.9198	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.06 [-0.03, 0.15], 0.1741		0.00 [-0.06, 0.07], 0.9194	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.2.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.5594		0.9844		0.4465	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	1/10 (10.0)	1/19 (5.3)	1/8 (12.5)	1/34 (2.9)	2/18 (11.1)
RR [95%-CI]; p-value	0.32 [0.01, 8.75], 0.5016		0.42 [0.03, 5.93], 0.5217		0.26 [0.03, 2.72], 0.2638	
OR [95%-CI]; p-value	0.30 [0.01, 9.87], 0.4778		0.39 [0.02, 7.11], 0.5121		0.24 [0.02, 2.88], 0.2293	
RD [95%-CI]; p-value	-0.07 [-0.27, 0.14], 0.5186		-0.07 [-0.32, 0.18], 0.5708		-0.08 [-0.24, 0.07], 0.3043	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	12/100 (12.0)	7/52 (13.5)	5/100 (5.0)	6/52 (11.5)	17/200 (8.5)	13/104 (12.5)
RR [95%-CI]; p-value	0.89 [0.37, 2.13], 0.7957		0.43 [0.14, 1.35], 0.1500		0.68 [0.34, 1.35], 0.2678	
OR [95%-CI]; p-value	0.88 [0.32, 2.38], 0.7960		0.40 [0.12, 1.39], 0.1399		0.65 [0.30, 1.40], 0.2673	
RD [95%-CI]; p-value	-0.01 [-0.13, 0.10], 0.7991		-0.07 [-0.16, 0.03], 0.1854		-0.04 [-0.11, 0.03], 0.2919	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_2_m_soc_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.4.s8.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.6285		0.6892		0.7842	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	3/10 (30.0)	2/19 (10.5)	0/8 (0.0)	2/34 (5.9)	3/18 (16.7)
RR [95%-CI]; p-value	0.11 [0.01, 1.93], 0.1300		1.79 [0.09, 35.64], 0.7030		0.35 [0.06, 1.92], 0.2286	
OR [95%-CI]; p-value	0.08 [0.00, 1.77], 0.0551		1.88 [0.08, 46.68], 0.6954		0.31 [0.05, 2.07], 0.2095	
RD [95%-CI]; p-value	-0.27 [-0.57, 0.03], 0.0776		0.05 [-0.16, 0.26], 0.6646		-0.11 [-0.30, 0.08], 0.2646	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	4/100 (4.0)	9/52 (17.3)	4/100 (4.0)	0/52 (0.0)	8/200 (4.0)	9/104 (8.7)
RR [95%-CI]; p-value	0.23 [0.07, 0.71], 0.0110		4.20 [0.23, 77.94], 0.3356		0.46 [0.18, 1.16], 0.1011	
OR [95%-CI]; p-value	0.20 [0.06, 0.68], 0.0054		4.33 [0.22, 83.56], 0.2907		0.44 [0.16, 1.18], 0.0939	
RD [95%-CI]; p-value	-0.13 [-0.24, -0.02], 0.0175		0.03 [-0.02, 0.08], 0.1993		-0.05 [-0.11, 0.01], 0.1315	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_4_m_pt_ae1pct_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.9164		0.2643		0.3322	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	2/19 (10.5)	3/8 (37.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.28 [0.06, 1.37], 0.1167		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.20 [0.03, 1.52], 0.0994		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	9/100 (9.0)	2/52 (3.8)	4/100 (4.0)	2/52 (3.8)	13/200 (6.5)	4/104 (3.8)
RR [95%-CI]; p-value	2.34 [0.52, 10.44], 0.2651		1.04 [0.20, 5.49], 0.9632		1.69 [0.57, 5.05], 0.3478	
OR [95%-CI]; p-value	2.47 [0.51, 11.89], 0.2446		1.04 [0.18, 5.88], 0.9631		1.74 [0.55, 5.47], 0.3394	
RD [95%-CI]; p-value	0.05 [-0.03, 0.13], 0.1877		0.00 [-0.06, 0.07], 0.9629		0.03 [-0.02, 0.08], 0.3014	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8666		NA		0.7995	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	0/52 (0.0)	0/100 (0.0)	0/52 (0.0)	1/200 (0.5)	0/104 (0.0)
RR [95%-CI]; p-value	1.05 [0.04, 30.79], 0.9774		NA		1.05 [0.04, 30.89], 0.9797	
OR [95%-CI]; p-value	1.05 [0.03, 31.84], 0.9774		NA		1.05 [0.03, 31.41], 0.9797	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9772		NA		0.00 [-0.02, 0.02], 0.9795	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.8622		0.2643		0.3803	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	2/19 (10.5)	3/8 (37.5)	4/34 (11.8)	3/18 (16.7)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		0.28 [0.06, 1.37], 0.1167		0.71 [0.18, 2.82], 0.6217	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		0.20 [0.03, 1.52], 0.0994		0.67 [0.13, 3.37], 0.6222	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		-0.27 [-0.63, 0.09], 0.1450		-0.05 [-0.25, 0.15], 0.6367	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	8/100 (8.0)	2/52 (3.8)	4/100 (4.0)	2/52 (3.8)	12/200 (6.0)	4/104 (3.8)
RR [95%-CI]; p-value	2.08 [0.46, 9.44], 0.3427		1.04 [0.20, 5.49], 0.9632		1.56 [0.52, 4.72], 0.4309	
OR [95%-CI]; p-value	2.17 [0.44, 10.63], 0.3271		1.04 [0.18, 5.88], 0.9631		1.60 [0.50, 5.08], 0.4250	
RD [95%-CI]; p-value	0.04 [-0.03, 0.12], 0.2749		0.00 [-0.06, 0.07], 0.9629		0.02 [-0.03, 0.07], 0.3937	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.5480		0.7361		0.4341	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	5/100 (5.0)	1/52 (1.9)	1/100 (1.0)	0/52 (0.0)	6/200 (3.0)	1/104 (1.0)
RR [95%-CI]; p-value	2.60 [0.31, 21.68], 0.3772		1.05 [0.04, 30.79], 0.9774		3.12 [0.38, 25.57], 0.2891	
OR [95%-CI]; p-value	2.68 [0.31, 23.60], 0.3554		1.05 [0.03, 31.84], 0.9774		3.19 [0.38, 26.82], 0.2609	
RD [95%-CI]; p-value	0.03 [-0.03, 0.09], 0.2877		0.00 [-0.03, 0.03], 0.9772		0.02 [-0.01, 0.05], 0.1855	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9150		0.3270		0.3575	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	3/15 (20.0)	3/10 (30.0)	0/19 (0.0)	1/8 (12.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.17, 2.67], 0.5664		0.21 [0.01, 5.53], 0.3458		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.58 [0.09, 3.72], 0.5663		0.18 [0.01, 6.12], 0.2974		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.10 [-0.45, 0.25], 0.5741		-0.10 [-0.34, 0.14], 0.4165		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	7/100 (7.0)	6/52 (11.5)	9/100 (9.0)	4/52 (7.7)	16/200 (8.0)	10/104 (9.6)
RR [95%-CI]; p-value	0.61 [0.21, 1.71], 0.3452		1.17 [0.38, 3.62], 0.7852		0.83 [0.39, 1.77], 0.6325	
OR [95%-CI]; p-value	0.58 [0.18, 1.82], 0.3425		1.19 [0.35, 4.05], 0.7845		0.82 [0.36, 1.87], 0.6328	
RD [95%-CI]; p-value	-0.05 [-0.15, 0.05], 0.3747		0.01 [-0.08, 0.10], 0.7796		-0.02 [-0.08, 0.05], 0.6415	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.8666		0.7057		0.6407	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	0/15 (0.0)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	0/34 (0.0)	0/18 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	1/100 (1.0)	0/52 (0.0)	2/100 (2.0)	1/52 (1.9)	3/200 (1.5)	1/104 (1.0)
RR [95%-CI]; p-value	1.05 [0.04, 30.79], 0.9774		1.04 [0.10, 11.20], 0.9742		1.56 [0.16, 14.81], 0.6986	
OR [95%-CI]; p-value	1.05 [0.03, 31.84], 0.9774		1.04 [0.09, 11.75], 0.9742		1.57 [0.16, 15.27], 0.6959	
RD [95%-CI]; p-value	0.00 [-0.03, 0.03], 0.9772		0.00 [-0.05, 0.05], 0.9740		0.01 [-0.02, 0.03], 0.6755	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.7817		0.3619		0.4539	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	3/15 (20.0)	3/10 (30.0)	0/19 (0.0)	1/8 (12.5)	3/34 (8.8)	4/18 (22.2)
RR [95%-CI]; p-value	0.67 [0.17, 2.67], 0.5664		0.21 [0.01, 5.53], 0.3458		0.40 [0.10, 1.58], 0.1907	
OR [95%-CI]; p-value	0.58 [0.09, 3.72], 0.5663		0.18 [0.01, 6.12], 0.2974		0.34 [0.07, 1.72], 0.1781	
RD [95%-CI]; p-value	-0.10 [-0.45, 0.25], 0.5741		-0.10 [-0.34, 0.14], 0.4165		-0.13 [-0.35, 0.08], 0.2207	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	6/100 (6.0)	6/52 (11.5)	8/100 (8.0)	4/52 (7.7)	14/200 (7.0)	10/104 (9.6)
RR [95%-CI]; p-value	0.52 [0.18, 1.53], 0.2357		1.04 [0.33, 3.29], 0.9468		0.73 [0.34, 1.58], 0.4228	
OR [95%-CI]; p-value	0.49 [0.15, 1.60], 0.2296		1.04 [0.30, 3.64], 0.9468		0.71 [0.30, 1.65], 0.4224	
RD [95%-CI]; p-value	-0.06 [-0.15, 0.04], 0.2706		0.00 [-0.09, 0.09], 0.9465		-0.03 [-0.09, 0.04], 0.4428	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.7.s8.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.8956		0.5737		0.9254	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	2/15 (13.3)	0/10 (0.0)	0/19 (0.0)	0/8 (0.0)	2/34 (5.9)	0/18 (0.0)
RR [95%-CI]; p-value	2.80 [0.14, 56.07], 0.5007		NA		2.18 [0.10, 45.81], 0.6169	
OR [95%-CI]; p-value	3.08 [0.12, 76.00], 0.4738		NA		2.25 [0.10, 52.63], 0.6053	
RD [95%-CI]; p-value	0.09 [-0.13, 0.30], 0.4344		NA		0.03 [-0.08, 0.14], 0.5648	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	2/100 (2.0)	0/52 (0.0)	3/100 (3.0)	1/52 (1.9)	5/200 (2.5)	1/104 (1.0)
RR [95%-CI]; p-value	2.10 [0.10, 45.73], 0.6369		1.56 [0.17, 14.63], 0.6970		2.60 [0.31, 21.96], 0.3802	
OR [95%-CI]; p-value	2.12 [0.09, 47.93], 0.6283		1.58 [0.16, 15.55], 0.6939		2.64 [0.30, 22.91], 0.3602	
RD [95%-CI]; p-value	0.01 [-0.03, 0.05], 0.5889		0.01 [-0.04, 0.06], 0.6736		0.02 [-0.01, 0.04], 0.2923	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_7_m_pt_smq_vitd_pp.sas using SAS 9.4

Table 12.4.4.1.6.s8.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Vitamin D Users vs 2.non-Vitamin D Users

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.2418		0.8845		0.6528	
1.Vitamin D Users	N1=15	N1=10	N1=19	N1=8	N1=34	N1=18
n/N1 (%)	1/15 (6.7)	4/10 (40.0)	7/19 (36.8)	2/8 (25.0)	8/34 (23.5)	6/18 (33.3)
RR [95%-CI]; p-value	0.17 [0.02, 1.28], 0.0852		1.47 [0.39, 5.61], 0.5697		0.71 [0.29, 1.72], 0.4436	
OR [95%-CI]; p-value	0.11 [0.01, 1.17], 0.0412		1.75 [0.27, 11.15], 0.5511		0.62 [0.17, 2.17], 0.4483	
RD [95%-CI]; p-value	-0.33 [-0.66, -0.00], 0.0469		0.12 [-0.25, 0.49], 0.5307		-0.10 [-0.36, 0.16], 0.4604	
2.non-Vitamin D Users	N2=100	N2=52	N2=100	N2=52	N2=200	N2=104
n/N2 (%)	15/100 (15.0)	13/52 (25.0)	16/100 (16.0)	5/52 (9.6)	31/200 (15.5)	18/104 (17.3)
RR [95%-CI]; p-value	0.60 [0.31, 1.16], 0.1309		1.66 [0.65, 4.29], 0.2917		0.90 [0.53, 1.52], 0.6835	
OR [95%-CI]; p-value	0.53 [0.23, 1.22], 0.1313		1.79 [0.62, 5.20], 0.2792		0.88 [0.46, 1.66], 0.6843	
RD [95%-CI]; p-value	-0.10 [-0.24, 0.04], 0.1523		0.06 [-0.04, 0.17], 0.2450		-0.02 [-0.11, 0.07], 0.6883	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s8_vitd_pp/T12_4_4_1_6_m_pt_adr_vitd_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE						
Interaction p-value	0.5637		0.9421		0.7639	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	47/58 (81.0)	30/35 (85.7)	37/59 (62.7)	19/30 (63.3)	84/117 (71.8)	49/65 (75.4)
RR [95%-CI]; p-value	0.95 [0.79, 1.14], 0.5494		0.99 [0.71, 1.39], 0.9541		0.95 [0.80, 1.14], 0.5941	
OR [95%-CI]; p-value	0.71 [0.23, 2.25], 0.5624		0.97 [0.39, 2.42], 0.9542		0.83 [0.42, 1.66], 0.6009	
RD [95%-CI]; p-value	-0.05 [-0.20, 0.11], 0.5506		-0.01 [-0.22, 0.21], 0.9542		-0.04 [-0.17, 0.10], 0.5960	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	36/57 (63.2)	20/27 (74.1)	35/60 (58.3)	18/30 (60.0)	71/117 (60.7)	38/57 (66.7)
RR [95%-CI]; p-value	0.85 [0.63, 1.15], 0.2952		0.97 [0.68, 1.40], 0.8788		0.91 [0.72, 1.15], 0.4318	
OR [95%-CI]; p-value	0.60 [0.22, 1.66], 0.3216		0.93 [0.38, 2.28], 0.8796		0.77 [0.40, 1.50], 0.4439	
RD [95%-CI]; p-value	-0.11 [-0.32, 0.10], 0.3022		-0.02 [-0.23, 0.20], 0.8793		-0.06 [-0.21, 0.09], 0.4375	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with drug-related AE						
Interaction p-value	0.1951		0.9264		0.5061	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	9/58 (15.5)	5/35 (14.3)	6/59 (10.2)	1/30 (3.3)	15/117 (12.8)	6/65 (9.2)
RR [95%-CI]; p-value	1.09 [0.40, 2.98], 0.8725		3.05 [0.38, 24.20], 0.2911		1.39 [0.57, 3.41], 0.4728	
OR [95%-CI]; p-value	1.10 [0.34, 3.60], 0.8722		3.28 [0.38, 28.61], 0.2574		1.45 [0.53, 3.93], 0.4676	
RD [95%-CI]; p-value	0.01 [-0.14, 0.16], 0.8711		0.07 [-0.03, 0.17], 0.1819		0.04 [-0.06, 0.13], 0.4486	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	5/27 (18.5)	7/60 (11.7)	1/30 (3.3)	11/117 (9.4)	6/57 (10.5)
RR [95%-CI]; p-value	0.38 [0.11, 1.30], 0.1228		3.50 [0.45, 27.16], 0.2308		0.89 [0.35, 2.29], 0.8143	
OR [95%-CI]; p-value	0.33 [0.08, 1.35], 0.1115		3.83 [0.45, 32.67], 0.1903		0.88 [0.31, 2.52], 0.8146	
RD [95%-CI]; p-value	-0.12 [-0.28, 0.05], 0.1610		0.08 [-0.02, 0.19], 0.1147		-0.01 [-0.11, 0.08], 0.8177	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with severe AE						
Interaction p-value	0.4937		0.1978		0.5504	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	3/35 (8.6)	2/59 (3.4)	1/30 (3.3)	8/117 (6.8)	4/65 (6.2)
RR [95%-CI]; p-value	1.21 [0.32, 4.52], 0.7802		1.02 [0.10, 10.77], 0.9889		1.11 [0.35, 3.55], 0.8589	
OR [95%-CI]; p-value	1.23 [0.29, 5.27], 0.7793		1.02 [0.09, 11.69], 0.9889		1.12 [0.32, 3.87], 0.8586	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7747		0.00 [-0.08, 0.08], 0.9888		0.01 [-0.07, 0.08], 0.8567	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	1/27 (3.7)	1/60 (1.7)	4/30 (13.3)	7/117 (6.0)	5/57 (8.8)
RR [95%-CI]; p-value	2.84 [0.36, 22.45], 0.3219		0.13 [0.01, 1.07], 0.0577		0.68 [0.23, 2.06], 0.4966	
OR [95%-CI]; p-value	3.06 [0.35, 26.76], 0.2907		0.11 [0.01, 1.03], 0.0227		0.66 [0.20, 2.18], 0.4956	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.2109		-0.12 [-0.24, 0.01], 0.0693		-0.03 [-0.11, 0.06], 0.5206	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with SAE						
Interaction p-value	0.5319		0.7361		0.5025	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	11/58 (19.0)	5/35 (14.3)	6/59 (10.2)	3/30 (10.0)	17/117 (14.5)	8/65 (12.3)
RR [95%-CI]; p-value	1.33 [0.50, 3.50], 0.5671		1.02 [0.27, 3.79], 0.9800		1.18 [0.54, 2.58], 0.6781	
OR [95%-CI]; p-value	1.40 [0.44, 4.44], 0.5624		1.02 [0.24, 4.39], 0.9800		1.21 [0.49, 2.98], 0.6765	
RD [95%-CI]; p-value	0.05 [-0.11, 0.20], 0.5506		0.00 [-0.13, 0.13], 0.9799		0.02 [-0.08, 0.12], 0.6701	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	9/57 (15.8)	5/27 (18.5)	6/60 (10.0)	4/30 (13.3)	15/117 (12.8)	9/57 (15.8)
RR [95%-CI]; p-value	0.85 [0.32, 2.30], 0.7529		0.75 [0.23, 2.46], 0.6347		0.81 [0.38, 1.74], 0.5928	
OR [95%-CI]; p-value	0.83 [0.25, 2.75], 0.7539		0.72 [0.19, 2.78], 0.6353		0.78 [0.32, 1.92], 0.5940	
RD [95%-CI]; p-value	-0.03 [-0.20, 0.15], 0.7591		-0.03 [-0.18, 0.11], 0.6486		-0.03 [-0.14, 0.08], 0.6046	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to treatment discontiuation						
Interaction p-value	0.1174		0.8582		0.1272	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	3/35 (8.6)	2/59 (3.4)	0/30 (0.0)	4/117 (3.4)	3/65 (4.6)
RR [95%-CI]; p-value	0.40 [0.07, 2.29], 0.3049		2.07 [0.10, 44.46], 0.6426		0.74 [0.17, 3.21], 0.6882	
OR [95%-CI]; p-value	0.38 [0.06, 2.40], 0.2886		2.11 [0.09, 48.17], 0.6338		0.73 [0.16, 3.37], 0.6875	
RD [95%-CI]; p-value	-0.05 [-0.16, 0.05], 0.3341		0.02 [-0.05, 0.08], 0.5949		-0.01 [-0.07, 0.05], 0.6993	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	0/27 (0.0)	3/60 (5.0)	0/30 (0.0)	9/117 (7.7)	0/57 (0.0)
RR [95%-CI]; p-value	5.79 [0.34, 99.97], 0.2270		3.05 [0.16, 58.98], 0.4606		8.85 [0.52, 149.93], 0.1311	
OR [95%-CI]; p-value	6.35 [0.34, 118.08], 0.1593		3.16 [0.15, 65.12], 0.4332		9.50 [0.54, 166.85], 0.0619	
RD [95%-CI]; p-value	0.09 [-0.01, 0.18], 0.0695		0.03 [-0.04, 0.10], 0.3550		0.07 [0.01, 0.12], 0.0131	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to study discontinuation						
Interaction p-value	0.9237		NA		0.9585	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	1/35 (2.9)	0/59 (0.0)	0/30 (0.0)	1/117 (0.9)	1/65 (1.5)
RR [95%-CI]; p-value	0.60 [0.04, 9.34], 0.7179		NA		0.56 [0.04, 8.74], 0.6758	
OR [95%-CI]; p-value	0.60 [0.04, 9.85], 0.7152		NA		0.55 [0.03, 8.97], 0.6716	
RD [95%-CI]; p-value	-0.01 [-0.08, 0.05], 0.7309		NA		-0.01 [-0.04, 0.03], 0.6956	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	0/30 (0.0)	0/117 (0.0)	0/57 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE leading to death						
Interaction p-value	0.8582		NA		0.8287	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	0/58 (0.0)	1/35 (2.9)	0/59 (0.0)	0/30 (0.0)	0/117 (0.0)	1/65 (1.5)
RR [95%-CI]; p-value	0.30 [0.01, 8.69], 0.4826		NA		0.28 [0.01, 8.13], 0.4563	
OR [95%-CI]; p-value	0.29 [0.01, 8.97], 0.4558		NA		0.27 [0.01, 8.26], 0.4252	
RD [95%-CI]; p-value	-0.02 [-0.08, 0.04], 0.5132		NA		-0.01 [-0.04, 0.02], 0.4975	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	0/30 (0.0)	0/117 (0.0)	0/57 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of patients with AE by severity						
Mild						
Interaction p-value	0.4950		0.1901		0.2469	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	41/58 (70.7)	28/35 (80.0)	31/59 (52.5)	12/30 (40.0)	72/117 (61.5)	40/65 (61.5)
RR [95%-CI]; p-value	0.88 [0.70, 1.12], 0.3007		1.31 [0.80, 2.17], 0.2859		1.00 [0.79, 1.27], 1.0000	
OR [95%-CI]; p-value	0.60 [0.22, 1.64], 0.3202		1.66 [0.68, 4.05], 0.2630		1.00 [0.54, 1.86], 1.0000	
RD [95%-CI]; p-value	-0.09 [-0.27, 0.08], 0.3022		0.13 [-0.09, 0.34], 0.2567		0.00 [-0.15, 0.15], 1.0000	
2.Baseline 25D ≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	27/57 (47.4)	17/27 (63.0)	29/60 (48.3)	17/30 (56.7)	56/117 (47.9)	34/57 (59.6)
RR [95%-CI]; p-value	0.75 [0.51, 1.12], 0.1613		0.85 [0.57, 1.28], 0.4447		0.80 [0.60, 1.07], 0.1304	
OR [95%-CI]; p-value	0.53 [0.21, 1.35], 0.1814		0.72 [0.30, 1.73], 0.4559		0.62 [0.33, 1.18], 0.1442	
RD [95%-CI]; p-value	-0.16 [-0.38, 0.07], 0.1716		-0.08 [-0.30, 0.13], 0.4533		-0.12 [-0.27, 0.04], 0.1393	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Moderate						
Interaction p-value	0.3599		0.4677		0.8796	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	21/58 (36.2)	13/35 (37.1)	19/59 (32.2)	10/30 (33.3)	40/117 (34.2)	23/65 (35.4)
RR [95%-CI]; p-value	0.97 [0.56, 1.69], 0.9275		0.97 [0.52, 1.81], 0.9142		0.97 [0.64, 1.46], 0.8705	
OR [95%-CI]; p-value	0.96 [0.40, 2.29], 0.9277		0.95 [0.37, 2.42], 0.9144		0.95 [0.50, 1.79], 0.8708	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.9277		-0.01 [-0.22, 0.20], 0.9146		-0.01 [-0.16, 0.13], 0.8711	
2.Baseline 25D ≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	17/57 (29.8)	12/27 (44.4)	17/60 (28.3)	6/30 (20.0)	34/117 (29.1)	18/57 (31.6)
RR [95%-CI]; p-value	0.67 [0.38, 1.20], 0.1777		1.42 [0.62, 3.22], 0.4057		0.92 [0.57, 1.48], 0.7319	
OR [95%-CI]; p-value	0.53 [0.21, 1.37], 0.1881		1.58 [0.55, 4.55], 0.3929		0.89 [0.45, 1.76], 0.7333	
RD [95%-CI]; p-value	-0.15 [-0.37, 0.08], 0.1966		0.08 [-0.10, 0.27], 0.3721		-0.03 [-0.17, 0.12], 0.7353	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.3.1.s9.pp
Overall Summary of Treatment-Emergent Adverse Events
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Severe						
Interaction p-value	0.4937		0.1978		0.5504	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	3/35 (8.6)	2/59 (3.4)	1/30 (3.3)	8/117 (6.8)	4/65 (6.2)
RR [95%-CI]; p-value	1.21 [0.32, 4.52], 0.7802		1.02 [0.10, 10.77], 0.9889		1.11 [0.35, 3.55], 0.8589	
OR [95%-CI]; p-value	1.23 [0.29, 5.27], 0.7793		1.02 [0.09, 11.69], 0.9889		1.12 [0.32, 3.87], 0.8586	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7747		0.00 [-0.08, 0.08], 0.9888		0.01 [-0.07, 0.08], 0.8567	
2.Baseline 25D ≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	1/27 (3.7)	1/60 (1.7)	4/30 (13.3)	7/117 (6.0)	5/57 (8.8)
RR [95%-CI]; p-value	2.84 [0.36, 22.45], 0.3219		0.13 [0.01, 1.07], 0.0577		0.68 [0.23, 2.06], 0.4966	
OR [95%-CI]; p-value	3.06 [0.35, 26.76], 0.2907		0.11 [0.01, 1.03], 0.0227		0.66 [0.20, 2.18], 0.4956	
RD [95%-CI]; p-value	0.07 [-0.04, 0.18], 0.2109		-0.12 [-0.24, 0.01], 0.0693		-0.03 [-0.11, 0.06], 0.5206	

Abbreviations: AE: Adverse Event; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_3_1_m_sf_ttl_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Cardiac disorders						
Interaction p-value	0.3222		0.5628		0.5919	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	7/35 (20.0)	5/59 (8.5)	1/30 (3.3)	9/117 (7.7)	8/65 (12.3)
RR [95%-CI]; p-value	0.34 [0.11, 1.09], 0.0707		2.54 [0.31, 20.79], 0.3842		0.63 [0.25, 1.54], 0.3076	
OR [95%-CI]; p-value	0.30 [0.08, 1.10], 0.0580		2.69 [0.30, 24.09], 0.3605		0.59 [0.22, 1.62], 0.3052	
RD [95%-CI]; p-value	-0.13 [-0.28, 0.02], 0.0821		0.05 [-0.04, 0.15], 0.2928		-0.05 [-0.14, 0.05], 0.3324	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	2/27 (7.4)	2/60 (3.3)	1/30 (3.3)	6/117 (5.1)	3/57 (5.3)
RR [95%-CI]; p-value	0.95 [0.18, 4.86], 0.9483		1.00 [0.09, 10.59], 1.0000		0.97 [0.25, 3.76], 0.9699	
OR [95%-CI]; p-value	0.94 [0.16, 5.50], 0.9483		1.00 [0.09, 11.49], 1.0000		0.97 [0.23, 4.04], 0.9699	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9488		0.00 [-0.08, 0.08], 1.0000		-0.00 [-0.07, 0.07], 0.9700	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.5872		0.7461		0.6028	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	12/58 (20.7)	10/35 (28.6)	13/59 (22.0)	3/30 (10.0)	25/117 (21.4)	13/65 (20.0)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3841		2.20 [0.68, 7.14], 0.1879		1.07 [0.59, 1.94], 0.8283	
OR [95%-CI]; p-value	0.65 [0.25, 1.72], 0.3862		2.54 [0.66, 9.74], 0.1622		1.09 [0.51, 2.30], 0.8278	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3970		0.12 [-0.03, 0.27], 0.1176		0.01 [-0.11, 0.14], 0.8266	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	9/57 (15.8)	8/27 (29.6)	10/60 (16.7)	3/30 (10.0)	19/117 (16.2)	11/57 (19.3)
RR [95%-CI]; p-value	0.53 [0.23, 1.23], 0.1396		1.67 [0.50, 5.61], 0.4093		0.84 [0.43, 1.65], 0.6146	
OR [95%-CI]; p-value	0.45 [0.15, 1.33], 0.1404		1.80 [0.46, 7.10], 0.3964		0.81 [0.36, 1.84], 0.6161	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.06], 0.1675		0.07 [-0.08, 0.21], 0.3605		-0.03 [-0.15, 0.09], 0.6240	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1180		0.5170		0.3182	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	5/35 (14.3)	8/59 (13.6)	5/30 (16.7)	16/117 (13.7)	10/65 (15.4)
RR [95%-CI]; p-value	0.97 [0.34, 2.72], 0.9470		0.81 [0.29, 2.27], 0.6938		0.89 [0.43, 1.84], 0.7517	
OR [95%-CI]; p-value	0.96 [0.29, 3.21], 0.9471		0.78 [0.23, 2.64], 0.6948		0.87 [0.37, 2.05], 0.7522	
RD [95%-CI]; p-value	-0.00 [-0.15, 0.14], 0.9473		-0.03 [-0.19, 0.13], 0.7024		-0.02 [-0.12, 0.09], 0.7554	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	10/27 (37.0)	6/60 (10.0)	2/30 (6.7)	13/117 (11.1)	12/57 (21.1)
RR [95%-CI]; p-value	0.33 [0.14, 0.78], 0.0110		1.50 [0.32, 6.99], 0.6056		0.53 [0.26, 1.08], 0.0810	
OR [95%-CI]; p-value	0.24 [0.08, 0.72], 0.0084		1.56 [0.29, 8.21], 0.6004		0.47 [0.20, 1.11], 0.0793	
RD [95%-CI]; p-value	-0.25 [-0.45, -0.05], 0.0158		0.03 [-0.08, 0.15], 0.5771		-0.10 [-0.22, 0.02], 0.1050	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.0385		0.2053		0.0193	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	21/58 (36.2)	8/35 (22.9)	17/59 (28.8)	6/30 (20.0)	38/117 (32.5)	14/65 (21.5)
RR [95%-CI]; p-value	1.58 [0.79, 3.18], 0.1964		1.44 [0.63, 3.27], 0.3831		1.51 [0.89, 2.57], 0.1306	
OR [95%-CI]; p-value	1.92 [0.74, 4.97], 0.1782		1.62 [0.56, 4.66], 0.3693		1.75 [0.86, 3.55], 0.1175	
RD [95%-CI]; p-value	0.13 [-0.05, 0.32], 0.1598		0.09 [-0.10, 0.27], 0.3477		0.11 [-0.02, 0.24], 0.1019	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	10/57 (17.5)	9/27 (33.3)	11/60 (18.3)	8/30 (26.7)	21/117 (17.9)	17/57 (29.8)
RR [95%-CI]; p-value	0.53 [0.24, 1.14], 0.1047		0.69 [0.31, 1.53], 0.3576		0.60 [0.35, 1.05], 0.0732	
OR [95%-CI]; p-value	0.43 [0.15, 1.22], 0.1062		0.62 [0.22, 1.75], 0.3611		0.51 [0.25, 1.08], 0.0752	
RD [95%-CI]; p-value	-0.16 [-0.36, 0.05], 0.1281		-0.08 [-0.27, 0.10], 0.3801		-0.12 [-0.26, 0.02], 0.0908	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.3563		0.8970		0.6983	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	10/58 (17.2)	6/35 (17.1)	4/59 (6.8)	2/30 (6.7)	14/117 (12.0)	8/65 (12.3)
RR [95%-CI]; p-value	1.01 [0.40, 2.53], 0.9903		1.02 [0.20, 5.24], 0.9840		0.97 [0.43, 2.19], 0.9459	
OR [95%-CI]; p-value	1.01 [0.33, 3.06], 0.9903		1.02 [0.18, 5.90], 0.9840		0.97 [0.38, 2.45], 0.9460	
RD [95%-CI]; p-value	0.00 [-0.16, 0.16], 0.9903		0.00 [-0.11, 0.11], 0.9839		-0.00 [-0.10, 0.10], 0.9461	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	4/27 (14.8)	7/60 (11.7)	3/30 (10.0)	11/117 (9.4)	7/57 (12.3)
RR [95%-CI]; p-value	0.47 [0.13, 1.75], 0.2629		1.17 [0.32, 4.19], 0.8133		0.77 [0.31, 1.87], 0.5577	
OR [95%-CI]; p-value	0.43 [0.10, 1.89], 0.2555		1.19 [0.28, 4.97], 0.8125		0.74 [0.27, 2.03], 0.5584	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3067		0.02 [-0.12, 0.15], 0.8083		-0.03 [-0.13, 0.07], 0.5737	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.6969		0.9614		0.6539	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	16/58 (27.6)	15/35 (42.9)	12/59 (20.3)	7/30 (23.3)	28/117 (23.9)	22/65 (33.8)
RR [95%-CI]; p-value	0.64 [0.37, 1.13], 0.1270		0.87 [0.38, 1.98], 0.7433		0.71 [0.44, 1.13], 0.1474	
OR [95%-CI]; p-value	0.51 [0.21, 1.23], 0.1302		0.84 [0.29, 2.41], 0.7445		0.61 [0.32, 1.20], 0.1511	
RD [95%-CI]; p-value	-0.15 [-0.35, 0.05], 0.1351		-0.03 [-0.21, 0.15], 0.7483		-0.10 [-0.24, 0.04], 0.1609	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	4/27 (14.8)	9/60 (15.0)	5/30 (16.7)	16/117 (13.7)	9/57 (15.8)
RR [95%-CI]; p-value	0.83 [0.27, 2.59], 0.7470		0.90 [0.33, 2.45], 0.8366		0.87 [0.41, 1.84], 0.7082	
OR [95%-CI]; p-value	0.81 [0.21, 3.03], 0.7478		0.88 [0.27, 2.91], 0.8371		0.84 [0.35, 2.05], 0.7090	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.13], 0.7544		-0.02 [-0.18, 0.14], 0.8393		-0.02 [-0.13, 0.09], 0.7146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0406		0.1652		0.0129	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	13/35 (37.1)	7/59 (11.9)	8/30 (26.7)	13/117 (11.1)	21/65 (32.3)
RR [95%-CI]; p-value	0.28 [0.12, 0.67], 0.0040		0.44 [0.18, 1.11], 0.0825		0.34 [0.18, 0.64], 0.0008	
OR [95%-CI]; p-value	0.20 [0.07, 0.58], 0.0019		0.37 [0.12, 1.15], 0.0778		0.26 [0.12, 0.57], 0.0004	
RD [95%-CI]; p-value	-0.27 [-0.45, -0.09], 0.0032		-0.15 [-0.33, 0.03], 0.1040		-0.21 [-0.34, -0.08], 0.0011	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	14/57 (24.6)	7/27 (25.9)	13/60 (21.7)	6/30 (20.0)	27/117 (23.1)	13/57 (22.8)
RR [95%-CI]; p-value	0.95 [0.43, 2.07], 0.8924		1.08 [0.46, 2.57], 0.8556		1.01 [0.57, 1.81], 0.9683	
OR [95%-CI]; p-value	0.93 [0.33, 2.66], 0.8927		1.11 [0.37, 3.27], 0.8551		1.02 [0.48, 2.16], 0.9683	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.8934		0.02 [-0.16, 0.19], 0.8536		0.00 [-0.13, 0.14], 0.9683	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8678		0.5567		0.6089	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	5/35 (14.3)	9/59 (15.3)	4/30 (13.3)	13/117 (11.1)	9/65 (13.8)
RR [95%-CI]; p-value	0.48 [0.14, 1.68], 0.2520		1.14 [0.38, 3.41], 0.8092		0.80 [0.36, 1.78], 0.5870	
OR [95%-CI]; p-value	0.44 [0.11, 1.78], 0.2429		1.17 [0.33, 4.16], 0.8084		0.78 [0.31, 1.93], 0.5876	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.06], 0.2762		0.02 [-0.13, 0.17], 0.8048		-0.03 [-0.13, 0.07], 0.5972	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	6/27 (22.2)	4/60 (6.7)	3/30 (10.0)	11/117 (9.4)	9/57 (15.8)
RR [95%-CI]; p-value	0.55 [0.21, 1.49], 0.2402		0.67 [0.16, 2.79], 0.5788		0.60 [0.26, 1.35], 0.2164	
OR [95%-CI]; p-value	0.49 [0.15, 1.63], 0.2394		0.64 [0.13, 3.08], 0.5778		0.55 [0.22, 1.42], 0.2150	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2749		-0.03 [-0.16, 0.09], 0.5998		-0.06 [-0.17, 0.04], 0.2482	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Psychiatric disorders						
Interaction p-value	0.5940		0.4292		0.8928	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	5/35 (14.3)	4/59 (6.8)	1/30 (3.3)	6/117 (5.1)	6/65 (9.2)
RR [95%-CI]; p-value	0.24 [0.05, 1.18], 0.0789		2.03 [0.24, 17.40], 0.5169		0.56 [0.19, 1.65], 0.2906	
OR [95%-CI]; p-value	0.21 [0.04, 1.17], 0.0550		2.11 [0.23, 19.75], 0.5045		0.53 [0.16, 1.72], 0.2852	
RD [95%-CI]; p-value	-0.11 [-0.23, 0.02], 0.0895		0.03 [-0.06, 0.13], 0.4568		-0.04 [-0.12, 0.04], 0.3204	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	2/27 (7.4)	1/60 (1.7)	1/30 (3.3)	3/117 (2.6)	3/57 (5.3)
RR [95%-CI]; p-value	0.47 [0.07, 3.19], 0.4422		0.50 [0.03, 7.72], 0.6196		0.49 [0.10, 2.34], 0.3689	
OR [95%-CI]; p-value	0.45 [0.06, 3.41], 0.4333		0.49 [0.03, 8.14], 0.6131		0.47 [0.09, 2.42], 0.3598	
RD [95%-CI]; p-value	-0.04 [-0.15, 0.07], 0.4862		-0.02 [-0.09, 0.06], 0.6498		-0.03 [-0.09, 0.04], 0.4133	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3941		0.1974		0.1774	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	9/58 (15.5)	5/35 (14.3)	7/59 (11.9)	1/30 (3.3)	16/117 (13.7)	6/65 (9.2)
RR [95%-CI]; p-value	1.09 [0.40, 2.98], 0.8725		3.56 [0.46, 27.61], 0.2245		1.48 [0.61, 3.60], 0.3856	
OR [95%-CI]; p-value	1.10 [0.34, 3.60], 0.8722		3.90 [0.46, 33.31], 0.1835		1.56 [0.58, 4.20], 0.3781	
RD [95%-CI]; p-value	0.01 [-0.14, 0.16], 0.8711		0.09 [-0.02, 0.19], 0.1098		0.04 [-0.05, 0.14], 0.3539	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	5/27 (18.5)	6/60 (10.0)	4/30 (13.3)	12/117 (10.3)	9/57 (15.8)
RR [95%-CI]; p-value	0.57 [0.19, 1.70], 0.3119		0.75 [0.23, 2.46], 0.6347		0.65 [0.29, 1.45], 0.2930	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3105		0.72 [0.19, 2.78], 0.6353		0.61 [0.24, 1.54], 0.2930	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3476		-0.03 [-0.18, 0.11], 0.6486		-0.06 [-0.16, 0.05], 0.3218	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0645		0.7078		0.1765	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	3/35 (8.6)	5/59 (8.5)	2/30 (6.7)	10/117 (8.5)	5/65 (7.7)
RR [95%-CI]; p-value	1.01 [0.26, 3.95], 0.9935		1.27 [0.26, 6.17], 0.7659		1.11 [0.40, 3.11], 0.8411	
OR [95%-CI]; p-value	1.01 [0.23, 4.50], 0.9935		1.30 [0.24, 7.11], 0.7646		1.12 [0.37, 3.43], 0.8408	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9934		0.02 [-0.10, 0.13], 0.7561		0.01 [-0.07, 0.09], 0.8386	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	5/27 (18.5)	7/60 (11.7)	4/30 (13.3)	8/117 (6.8)	9/57 (15.8)
RR [95%-CI]; p-value	0.09 [0.01, 0.77], 0.0277		0.88 [0.28, 2.76], 0.8196		0.43 [0.18, 1.06], 0.0678	
OR [95%-CI]; p-value	0.08 [0.01, 0.71], 0.0053		0.86 [0.23, 3.20], 0.8200		0.39 [0.14, 1.08], 0.0620	
RD [95%-CI]; p-value	-0.17 [-0.32, -0.02], 0.0289		-0.02 [-0.16, 0.13], 0.8233		-0.09 [-0.19, 0.02], 0.0951	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.1.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8663		0.7037		0.8526	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	6/35 (17.1)	4/59 (6.8)	4/30 (13.3)	12/117 (10.3)	10/65 (15.4)
RR [95%-CI]; p-value	0.80 [0.30, 2.13], 0.6610		0.51 [0.14, 1.89], 0.3132		0.67 [0.30, 1.46], 0.3098	
OR [95%-CI]; p-value	0.77 [0.24, 2.45], 0.6616		0.47 [0.11, 2.04], 0.3069		0.63 [0.26, 1.55], 0.3092	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.12], 0.6682		-0.07 [-0.20, 0.07], 0.3503		-0.05 [-0.15, 0.05], 0.3316	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	2/27 (7.4)	2/60 (3.3)	3/30 (10.0)	6/117 (5.1)	5/57 (8.8)
RR [95%-CI]; p-value	0.95 [0.18, 4.86], 0.9483		0.33 [0.06, 1.89], 0.2145		0.58 [0.19, 1.83], 0.3577	
OR [95%-CI]; p-value	0.94 [0.16, 5.50], 0.9483		0.31 [0.05, 1.97], 0.1931		0.56 [0.16, 1.93], 0.3539	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9488		-0.07 [-0.18, 0.05], 0.2623		-0.04 [-0.12, 0.05], 0.3930	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_1_m_soc_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.3.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9325		0.7420		0.8120	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	7/35 (20.0)	4/59 (6.8)	0/30 (0.0)	6/117 (5.1)	7/65 (10.8)
RR [95%-CI]; p-value	0.17 [0.04, 0.78], 0.0229		4.14 [0.23, 75.71], 0.3385		0.48 [0.17, 1.36], 0.1650	
OR [95%-CI]; p-value	0.14 [0.03, 0.73], 0.0089		4.36 [0.22, 85.35], 0.2915		0.45 [0.14, 1.39], 0.1568	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0210		0.05 [-0.03, 0.13], 0.1987		-0.06 [-0.14, 0.03], 0.1949	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	5/27 (18.5)	2/60 (3.3)	0/30 (0.0)	4/117 (3.4)	5/57 (8.8)
RR [95%-CI]; p-value	0.19 [0.04, 0.91], 0.0384		2.03 [0.09, 43.72], 0.6503		0.39 [0.11, 1.40], 0.1478	
OR [95%-CI]; p-value	0.16 [0.03, 0.89], 0.0201		2.07 [0.09, 47.33], 0.6421		0.37 [0.09, 1.43], 0.1345	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0563		0.02 [-0.05, 0.08], 0.6038		-0.05 [-0.13, 0.03], 0.1924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_3_m_pt_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.3.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Urinary tract infection						
Interaction p-value	0.5323		0.7750		0.9520	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	3/58 (5.2)	5/35 (14.3)	2/59 (3.4)	0/30 (0.0)	5/117 (4.3)	5/65 (7.7)
RR [95%-CI]; p-value	0.36 [0.09, 1.42], 0.1457		2.07 [0.10, 44.46], 0.6426		0.56 [0.17, 1.85], 0.3378	
OR [95%-CI]; p-value	0.33 [0.07, 1.47], 0.1289		2.11 [0.09, 48.17], 0.6338		0.54 [0.15, 1.92], 0.3321	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.04], 0.1668		0.02 [-0.05, 0.08], 0.5949		-0.03 [-0.11, 0.04], 0.3680	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	3/27 (11.1)	5/60 (8.3)	2/30 (6.7)	6/117 (5.1)	5/57 (8.8)
RR [95%-CI]; p-value	0.16 [0.02, 1.45], 0.1026		1.25 [0.26, 6.07], 0.7820		0.58 [0.19, 1.83], 0.3577	
OR [95%-CI]; p-value	0.14 [0.01, 1.44], 0.0600		1.27 [0.23, 6.98], 0.7808		0.56 [0.16, 1.93], 0.3539	
RD [95%-CI]; p-value	-0.09 [-0.22, 0.03], 0.1371		0.02 [-0.10, 0.13], 0.7733		-0.04 [-0.12, 0.05], 0.3930	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_3_m_pt_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.3.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Hypertension						
Interaction p-value	0.8606		0.7643		0.6817	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	3/35 (8.6)	3/59 (5.1)	4/30 (13.3)	9/117 (7.7)	7/65 (10.8)
RR [95%-CI]; p-value	1.21 [0.32, 4.52], 0.7802		0.38 [0.09, 1.60], 0.1867		0.71 [0.28, 1.83], 0.4830	
OR [95%-CI]; p-value	1.23 [0.29, 5.27], 0.7793		0.35 [0.07, 1.67], 0.1718		0.69 [0.24, 1.95], 0.4824	
RD [95%-CI]; p-value	0.02 [-0.10, 0.14], 0.7747		-0.08 [-0.22, 0.05], 0.2274		-0.03 [-0.12, 0.06], 0.5004	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	1/27 (3.7)	1/60 (1.7)	2/30 (6.7)	3/117 (2.6)	3/57 (5.3)
RR [95%-CI]; p-value	0.95 [0.09, 10.00], 0.9641		0.25 [0.02, 2.65], 0.2496		0.49 [0.10, 2.34], 0.3689	
OR [95%-CI]; p-value	0.95 [0.08, 10.91], 0.9641		0.24 [0.02, 2.73], 0.2129		0.47 [0.09, 2.42], 0.3598	
RD [95%-CI]; p-value	-0.00 [-0.09, 0.08], 0.9645		-0.05 [-0.14, 0.04], 0.3021		-0.03 [-0.09, 0.04], 0.4133	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_3_m_pt_ae10pct_bl25d_pp.sas using SAS 9.4

Table 12.4.8.1.1.s9.pp
Summary of SAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.6680		0.3839		0.5221	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	0/35 (0.0)	1/59 (1.7)	3/30 (10.0)	2/117 (1.7)	3/65 (4.6)
RR [95%-CI]; p-value	1.22 [0.04, 35.56], 0.9063		0.17 [0.02, 1.56], 0.1171		0.37 [0.06, 2.16], 0.2696	
OR [95%-CI]; p-value	1.23 [0.04, 37.57], 0.9061		0.16 [0.02, 1.56], 0.0738		0.36 [0.06, 2.21], 0.2505	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9039		-0.08 [-0.20, 0.03], 0.1472		-0.03 [-0.09, 0.03], 0.3105	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	1/27 (3.7)	1/60 (1.7)	0/30 (0.0)	2/117 (1.7)	1/57 (1.8)
RR [95%-CI]; p-value	0.47 [0.03, 7.29], 0.5922		1.02 [0.04, 29.46], 0.9923		0.97 [0.09, 10.52], 0.9829	
OR [95%-CI]; p-value	0.46 [0.03, 7.72], 0.5842		1.02 [0.03, 31.18], 0.9923		0.97 [0.09, 10.97], 0.9829	
RD [95%-CI]; p-value	-0.02 [-0.10, 0.06], 0.6285		0.00 [-0.06, 0.06], 0.9923		-0.00 [-0.04, 0.04], 0.9830	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_8_1_1_m_soc_sae5pct_bl25d_pp.sas using SAS 9.4

Table 12.4.8.1.2.s9.pp
Summary of SAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SAE: Serious Adverse Event; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_8_1_2_m_pt_sae5pct_bl25d_pp.sas using SAS 9.4

Table 12.4.5.1.1.s9.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_5_1_1_m_soc_aeg35pct_bl25d_pp.sas using SAS 9.4

Table 12.4.5.1.2.s9.pp
Summary of severe TEAE Occurring ≥ 5 % in One Arm by PT
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

No data satisfy criteria

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_5_1_2_m_pt_aeg35pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Interaction p-value	0.5872		0.7461		0.6028	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	12/58 (20.7)	10/35 (28.6)	13/59 (22.0)	3/30 (10.0)	25/117 (21.4)	13/65 (20.0)
RR [95%-CI]; p-value	0.72 [0.35, 1.50], 0.3841		2.20 [0.68, 7.14], 0.1879		1.07 [0.59, 1.94], 0.8283	
OR [95%-CI]; p-value	0.65 [0.25, 1.72], 0.3862		2.54 [0.66, 9.74], 0.1622		1.09 [0.51, 2.30], 0.8278	
RD [95%-CI]; p-value	-0.08 [-0.26, 0.10], 0.3970		0.12 [-0.03, 0.27], 0.1176		0.01 [-0.11, 0.14], 0.8266	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	9/57 (15.8)	8/27 (29.6)	10/60 (16.7)	3/30 (10.0)	19/117 (16.2)	11/57 (19.3)
RR [95%-CI]; p-value	0.53 [0.23, 1.23], 0.1396		1.67 [0.50, 5.61], 0.4093		0.84 [0.43, 1.65], 0.6146	
OR [95%-CI]; p-value	0.45 [0.15, 1.33], 0.1404		1.80 [0.46, 7.10], 0.3964		0.81 [0.36, 1.84], 0.6161	
RD [95%-CI]; p-value	-0.14 [-0.33, 0.06], 0.1675		0.07 [-0.08, 0.21], 0.3605		-0.03 [-0.15, 0.09], 0.6240	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
General disorders and administration site conditions						
Interaction p-value	0.1180		0.5170		0.3182	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	5/35 (14.3)	8/59 (13.6)	5/30 (16.7)	16/117 (13.7)	10/65 (15.4)
RR [95%-CI]; p-value	0.97 [0.34, 2.72], 0.9470		0.81 [0.29, 2.27], 0.6938		0.89 [0.43, 1.84], 0.7517	
OR [95%-CI]; p-value	0.96 [0.29, 3.21], 0.9471		0.78 [0.23, 2.64], 0.6948		0.87 [0.37, 2.05], 0.7522	
RD [95%-CI]; p-value	-0.00 [-0.15, 0.14], 0.9473		-0.03 [-0.19, 0.13], 0.7024		-0.02 [-0.12, 0.09], 0.7554	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	10/27 (37.0)	6/60 (10.0)	2/30 (6.7)	13/117 (11.1)	12/57 (21.1)
RR [95%-CI]; p-value	0.33 [0.14, 0.78], 0.0110		1.50 [0.32, 6.99], 0.6056		0.53 [0.26, 1.08], 0.0810	
OR [95%-CI]; p-value	0.24 [0.08, 0.72], 0.0084		1.56 [0.29, 8.21], 0.6004		0.47 [0.20, 1.11], 0.0793	
RD [95%-CI]; p-value	-0.25 [-0.45, -0.05], 0.0158		0.03 [-0.08, 0.15], 0.5771		-0.10 [-0.22, 0.02], 0.1050	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Infections and infestations						
Interaction p-value	0.0385		0.2053		0.0193	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	21/58 (36.2)	8/35 (22.9)	17/59 (28.8)	6/30 (20.0)	38/117 (32.5)	14/65 (21.5)
RR [95%-CI]; p-value	1.58 [0.79, 3.18], 0.1964		1.44 [0.63, 3.27], 0.3831		1.51 [0.89, 2.57], 0.1306	
OR [95%-CI]; p-value	1.92 [0.74, 4.97], 0.1782		1.62 [0.56, 4.66], 0.3693		1.75 [0.86, 3.55], 0.1175	
RD [95%-CI]; p-value	0.13 [-0.05, 0.32], 0.1598		0.09 [-0.10, 0.27], 0.3477		0.11 [-0.02, 0.24], 0.1019	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	10/57 (17.5)	9/27 (33.3)	11/60 (18.3)	8/30 (26.7)	21/117 (17.9)	17/57 (29.8)
RR [95%-CI]; p-value	0.53 [0.24, 1.14], 0.1047		0.69 [0.31, 1.53], 0.3576		0.60 [0.35, 1.05], 0.0732	
OR [95%-CI]; p-value	0.43 [0.15, 1.22], 0.1062		0.62 [0.22, 1.75], 0.3611		0.51 [0.25, 1.08], 0.0752	
RD [95%-CI]; p-value	-0.16 [-0.36, 0.05], 0.1281		-0.08 [-0.27, 0.10], 0.3801		-0.12 [-0.26, 0.02], 0.0908	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Injury, poisoning and procedural complications						
Interaction p-value	0.4347		0.1560		0.0865	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	4/35 (11.4)	2/59 (3.4)	2/30 (6.7)	8/117 (6.8)	6/65 (9.2)
RR [95%-CI]; p-value	0.91 [0.27, 2.99], 0.8700		0.51 [0.08, 3.43], 0.4877		0.74 [0.27, 2.04], 0.5619	
OR [95%-CI]; p-value	0.89 [0.23, 3.42], 0.8702		0.49 [0.07, 3.67], 0.4806		0.72 [0.24, 2.18], 0.5615	
RD [95%-CI]; p-value	-0.01 [-0.14, 0.12], 0.8715		-0.03 [-0.13, 0.07], 0.5228		-0.02 [-0.11, 0.06], 0.5762	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	1/27 (3.7)	6/60 (10.0)	0/30 (0.0)	11/117 (9.4)	1/57 (1.8)
RR [95%-CI]; p-value	2.37 [0.29, 19.30], 0.4205		6.10 [0.35, 105.65], 0.2140		5.36 [0.71, 40.50], 0.1038	
OR [95%-CI]; p-value	2.50 [0.28, 22.52], 0.3996		6.67 [0.36, 123.52], 0.1454		5.81 [0.73, 46.17], 0.0617	
RD [95%-CI]; p-value	0.05 [-0.05, 0.15], 0.3316		0.08 [-0.00, 0.17], 0.0634		0.08 [0.01, 0.14], 0.0172	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Investigations						
Interaction p-value	0.3563		0.8970		0.6983	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	10/58 (17.2)	6/35 (17.1)	4/59 (6.8)	2/30 (6.7)	14/117 (12.0)	8/65 (12.3)
RR [95%-CI]; p-value	1.01 [0.40, 2.53], 0.9903		1.02 [0.20, 5.24], 0.9840		0.97 [0.43, 2.19], 0.9459	
OR [95%-CI]; p-value	1.01 [0.33, 3.06], 0.9903		1.02 [0.18, 5.90], 0.9840		0.97 [0.38, 2.45], 0.9460	
RD [95%-CI]; p-value	0.00 [-0.16, 0.16], 0.9903		0.00 [-0.11, 0.11], 0.9839		-0.00 [-0.10, 0.10], 0.9461	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	4/27 (14.8)	7/60 (11.7)	3/30 (10.0)	11/117 (9.4)	7/57 (12.3)
RR [95%-CI]; p-value	0.47 [0.13, 1.75], 0.2629		1.17 [0.32, 4.19], 0.8133		0.77 [0.31, 1.87], 0.5577	
OR [95%-CI]; p-value	0.43 [0.10, 1.89], 0.2555		1.19 [0.28, 4.97], 0.8125		0.74 [0.27, 2.03], 0.5584	
RD [95%-CI]; p-value	-0.08 [-0.23, 0.07], 0.3067		0.02 [-0.12, 0.15], 0.8083		-0.03 [-0.13, 0.07], 0.5737	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Metabolism and nutrition disorders						
Interaction p-value	0.6969		0.9614		0.6539	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	16/58 (27.6)	15/35 (42.9)	12/59 (20.3)	7/30 (23.3)	28/117 (23.9)	22/65 (33.8)
RR [95%-CI]; p-value	0.64 [0.37, 1.13], 0.1270		0.87 [0.38, 1.98], 0.7433		0.71 [0.44, 1.13], 0.1474	
OR [95%-CI]; p-value	0.51 [0.21, 1.23], 0.1302		0.84 [0.29, 2.41], 0.7445		0.61 [0.32, 1.20], 0.1511	
RD [95%-CI]; p-value	-0.15 [-0.35, 0.05], 0.1351		-0.03 [-0.21, 0.15], 0.7483		-0.10 [-0.24, 0.04], 0.1609	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	4/27 (14.8)	9/60 (15.0)	5/30 (16.7)	16/117 (13.7)	9/57 (15.8)
RR [95%-CI]; p-value	0.83 [0.27, 2.59], 0.7470		0.90 [0.33, 2.45], 0.8366		0.87 [0.41, 1.84], 0.7082	
OR [95%-CI]; p-value	0.81 [0.21, 3.03], 0.7478		0.88 [0.27, 2.91], 0.8371		0.84 [0.35, 2.05], 0.7090	
RD [95%-CI]; p-value	-0.03 [-0.18, 0.13], 0.7544		-0.02 [-0.18, 0.14], 0.8393		-0.02 [-0.13, 0.09], 0.7146	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Musculoskeletal and connective tissue disorders						
Interaction p-value	0.0406		0.1652		0.0129	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	13/35 (37.1)	7/59 (11.9)	8/30 (26.7)	13/117 (11.1)	21/65 (32.3)
RR [95%-CI]; p-value	0.28 [0.12, 0.67], 0.0040		0.44 [0.18, 1.11], 0.0825		0.34 [0.18, 0.64], 0.0008	
OR [95%-CI]; p-value	0.20 [0.07, 0.58], 0.0019		0.37 [0.12, 1.15], 0.0778		0.26 [0.12, 0.57], 0.0004	
RD [95%-CI]; p-value	-0.27 [-0.45, -0.09], 0.0032		-0.15 [-0.33, 0.03], 0.1040		-0.21 [-0.34, -0.08], 0.0011	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	14/57 (24.6)	7/27 (25.9)	13/60 (21.7)	6/30 (20.0)	27/117 (23.1)	13/57 (22.8)
RR [95%-CI]; p-value	0.95 [0.43, 2.07], 0.8924		1.08 [0.46, 2.57], 0.8556		1.01 [0.57, 1.81], 0.9683	
OR [95%-CI]; p-value	0.93 [0.33, 2.66], 0.8927		1.11 [0.37, 3.27], 0.8551		1.02 [0.48, 2.16], 0.9683	
RD [95%-CI]; p-value	-0.01 [-0.21, 0.19], 0.8934		0.02 [-0.16, 0.19], 0.8536		0.00 [-0.13, 0.14], 0.9683	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Nervous system disorders						
Interaction p-value	0.8678		0.5567		0.6089	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	5/35 (14.3)	9/59 (15.3)	4/30 (13.3)	13/117 (11.1)	9/65 (13.8)
RR [95%-CI]; p-value	0.48 [0.14, 1.68], 0.2520		1.14 [0.38, 3.41], 0.8092		0.80 [0.36, 1.78], 0.5870	
OR [95%-CI]; p-value	0.44 [0.11, 1.78], 0.2429		1.17 [0.33, 4.16], 0.8084		0.78 [0.31, 1.93], 0.5876	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.06], 0.2762		0.02 [-0.13, 0.17], 0.8048		-0.03 [-0.13, 0.07], 0.5972	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	7/57 (12.3)	6/27 (22.2)	4/60 (6.7)	3/30 (10.0)	11/117 (9.4)	9/57 (15.8)
RR [95%-CI]; p-value	0.55 [0.21, 1.49], 0.2402		0.67 [0.16, 2.79], 0.5788		0.60 [0.26, 1.35], 0.2164	
OR [95%-CI]; p-value	0.49 [0.15, 1.63], 0.2394		0.64 [0.13, 3.08], 0.5778		0.55 [0.22, 1.42], 0.2150	
RD [95%-CI]; p-value	-0.10 [-0.28, 0.08], 0.2749		-0.03 [-0.16, 0.09], 0.5998		-0.06 [-0.17, 0.04], 0.2482	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Respiratory, thoracic and mediastinal disorders						
Interaction p-value	0.3941		0.1974		0.1774	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	9/58 (15.5)	5/35 (14.3)	7/59 (11.9)	1/30 (3.3)	16/117 (13.7)	6/65 (9.2)
RR [95%-CI]; p-value	1.09 [0.40, 2.98], 0.8725		3.56 [0.46, 27.61], 0.2245		1.48 [0.61, 3.60], 0.3856	
OR [95%-CI]; p-value	1.10 [0.34, 3.60], 0.8722		3.90 [0.46, 33.31], 0.1835		1.56 [0.58, 4.20], 0.3781	
RD [95%-CI]; p-value	0.01 [-0.14, 0.16], 0.8711		0.09 [-0.02, 0.19], 0.1098		0.04 [-0.05, 0.14], 0.3539	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	6/57 (10.5)	5/27 (18.5)	6/60 (10.0)	4/30 (13.3)	12/117 (10.3)	9/57 (15.8)
RR [95%-CI]; p-value	0.57 [0.19, 1.70], 0.3119		0.75 [0.23, 2.46], 0.6347		0.65 [0.29, 1.45], 0.2930	
OR [95%-CI]; p-value	0.52 [0.14, 1.88], 0.3105		0.72 [0.19, 2.78], 0.6353		0.61 [0.24, 1.54], 0.2930	
RD [95%-CI]; p-value	-0.08 [-0.25, 0.09], 0.3476		-0.03 [-0.18, 0.11], 0.6486		-0.06 [-0.16, 0.05], 0.3218	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Skin and subcutaneous tissue disorders						
Interaction p-value	0.0645		0.7078		0.1765	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	3/35 (8.6)	5/59 (8.5)	2/30 (6.7)	10/117 (8.5)	5/65 (7.7)
RR [95%-CI]; p-value	1.01 [0.26, 3.95], 0.9935		1.27 [0.26, 6.17], 0.7659		1.11 [0.40, 3.11], 0.8411	
OR [95%-CI]; p-value	1.01 [0.23, 4.50], 0.9935		1.30 [0.24, 7.11], 0.7646		1.12 [0.37, 3.43], 0.8408	
RD [95%-CI]; p-value	0.00 [-0.12, 0.12], 0.9934		0.02 [-0.10, 0.13], 0.7561		0.01 [-0.07, 0.09], 0.8386	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	1/57 (1.8)	5/27 (18.5)	7/60 (11.7)	4/30 (13.3)	8/117 (6.8)	9/57 (15.8)
RR [95%-CI]; p-value	0.09 [0.01, 0.77], 0.0277		0.88 [0.28, 2.76], 0.8196		0.43 [0.18, 1.06], 0.0678	
OR [95%-CI]; p-value	0.08 [0.01, 0.71], 0.0053		0.86 [0.23, 3.20], 0.8200		0.39 [0.14, 1.08], 0.0620	
RD [95%-CI]; p-value	-0.17 [-0.32, -0.02], 0.0289		-0.02 [-0.16, 0.13], 0.8233		-0.09 [-0.19, 0.02], 0.0951	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.2.s9.pp
Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by SOC
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Vascular disorders						
Interaction p-value	0.8663		0.7037		0.8526	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	6/35 (17.1)	4/59 (6.8)	4/30 (13.3)	12/117 (10.3)	10/65 (15.4)
RR [95%-CI]; p-value	0.80 [0.30, 2.13], 0.6610		0.51 [0.14, 1.89], 0.3132		0.67 [0.30, 1.46], 0.3098	
OR [95%-CI]; p-value	0.77 [0.24, 2.45], 0.6616		0.47 [0.11, 2.04], 0.3069		0.63 [0.26, 1.55], 0.3092	
RD [95%-CI]; p-value	-0.03 [-0.19, 0.12], 0.6682		-0.07 [-0.20, 0.07], 0.3503		-0.05 [-0.15, 0.05], 0.3316	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	4/57 (7.0)	2/27 (7.4)	2/60 (3.3)	3/30 (10.0)	6/117 (5.1)	5/57 (8.8)
RR [95%-CI]; p-value	0.95 [0.18, 4.86], 0.9483		0.33 [0.06, 1.89], 0.2145		0.58 [0.19, 1.83], 0.3577	
OR [95%-CI]; p-value	0.94 [0.16, 5.50], 0.9483		0.31 [0.05, 1.97], 0.1931		0.56 [0.16, 1.93], 0.3539	
RD [95%-CI]; p-value	-0.00 [-0.12, 0.12], 0.9488		-0.07 [-0.18, 0.05], 0.2623		-0.04 [-0.12, 0.05], 0.3930	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_2_m_soc_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.4.s9.pp

Summary of TEAE (independent of severity) Occurring≥ 10 Patients AND ≥ 1 % in One Arm by PT

PP Population

Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Gastrointestinal disorders						
Diarrhoea						
Interaction p-value	0.9325		0.7420		0.8120	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	7/35 (20.0)	4/59 (6.8)	0/30 (0.0)	6/117 (5.1)	7/65 (10.8)
RR [95%-CI]; p-value	0.17 [0.04, 0.78], 0.0229		4.14 [0.23, 75.71], 0.3385		0.48 [0.17, 1.36], 0.1650	
OR [95%-CI]; p-value	0.14 [0.03, 0.73], 0.0089		4.36 [0.22, 85.35], 0.2915		0.45 [0.14, 1.39], 0.1568	
RD [95%-CI]; p-value	-0.17 [-0.31, -0.02], 0.0210		0.05 [-0.03, 0.13], 0.1987		-0.06 [-0.14, 0.03], 0.1949	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	5/27 (18.5)	2/60 (3.3)	0/30 (0.0)	4/117 (3.4)	5/57 (8.8)
RR [95%-CI]; p-value	0.19 [0.04, 0.91], 0.0384		2.03 [0.09, 43.72], 0.6503		0.39 [0.11, 1.40], 0.1478	
OR [95%-CI]; p-value	0.16 [0.03, 0.89], 0.0201		2.07 [0.09, 47.33], 0.6421		0.37 [0.09, 1.43], 0.1345	
RD [95%-CI]; p-value	-0.15 [-0.30, 0.00], 0.0563		0.02 [-0.05, 0.08], 0.6038		-0.05 [-0.13, 0.03], 0.1924	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.

25 D: 25-Hydroxyvitamin D.

Source: Listing 14.6.1

Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.

N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.

S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_4_m_pt_ae1pct_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Acute Renal Failure						
Interaction p-value	0.5557		0.7212		0.9649	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	6/58 (10.3)	2/35 (5.7)	3/59 (5.1)	2/30 (6.7)	9/117 (7.7)	4/65 (6.2)
RR [95%-CI]; p-value	1.81 [0.39, 8.48], 0.4513		0.76 [0.13, 4.32], 0.7595		1.25 [0.40, 3.90], 0.7008	
OR [95%-CI]; p-value	1.90 [0.36, 10.00], 0.4404		0.75 [0.12, 4.75], 0.7593		1.27 [0.38, 4.30], 0.6994	
RD [95%-CI]; p-value	0.05 [-0.06, 0.16], 0.4085		-0.02 [-0.12, 0.09], 0.7686		0.02 [-0.06, 0.09], 0.6907	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	0/27 (0.0)	3/60 (5.0)	3/30 (10.0)	8/117 (6.8)	3/57 (5.3)
RR [95%-CI]; p-value	4.82 [0.27, 85.20], 0.2827		0.50 [0.11, 2.33], 0.3774		1.30 [0.36, 4.71], 0.6906	
OR [95%-CI]; p-value	5.19 [0.27, 98.61], 0.2247		0.47 [0.09, 2.50], 0.3700		1.32 [0.34, 5.18], 0.6888	
RD [95%-CI]; p-value	0.07 [-0.02, 0.16], 0.1249		-0.05 [-0.17, 0.07], 0.4168		0.02 [-0.06, 0.09], 0.6760	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Acute Renal Failure						
Interaction p-value	0.7205		NA		0.7536	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	0/35 (0.0)	0/59 (0.0)	0/30 (0.0)	1/117 (0.9)	0/65 (0.0)
RR [95%-CI]; p-value	1.22 [0.04, 35.56], 0.9063		NA		1.12 [0.04, 32.93], 0.9478	
OR [95%-CI]; p-value	1.23 [0.04, 37.57], 0.9061		NA		1.12 [0.04, 33.86], 0.9477	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9039		NA		0.00 [-0.03, 0.03], 0.9469	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	0/30 (0.0)	0/117 (0.0)	0/57 (0.0)
RR [95%-CI]; p-value	NA		NA		NA	
OR [95%-CI]; p-value	NA		NA		NA	
RD [95%-CI]; p-value	NA		NA		NA	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Acute Renal Failure						
Interaction p-value	0.4872		0.7212		0.8598	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	2/35 (5.7)	3/59 (5.1)	2/30 (6.7)	8/117 (6.8)	4/65 (6.2)
RR [95%-CI]; p-value	1.51 [0.31, 7.36], 0.6112		0.76 [0.13, 4.32], 0.7595		1.11 [0.35, 3.55], 0.8589	
OR [95%-CI]; p-value	1.56 [0.29, 8.49], 0.6068		0.75 [0.12, 4.75], 0.7593		1.12 [0.32, 3.87], 0.8586	
RD [95%-CI]; p-value	0.03 [-0.08, 0.13], 0.5892		-0.02 [-0.12, 0.09], 0.7686		0.01 [-0.07, 0.08], 0.8567	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	0/27 (0.0)	3/60 (5.0)	3/30 (10.0)	8/117 (6.8)	3/57 (5.3)
RR [95%-CI]; p-value	4.82 [0.27, 85.20], 0.2827		0.50 [0.11, 2.33], 0.3774		1.30 [0.36, 4.71], 0.6906	
OR [95%-CI]; p-value	5.19 [0.27, 98.61], 0.2247		0.47 [0.09, 2.50], 0.3700		1.32 [0.34, 5.18], 0.6888	
RD [95%-CI]; p-value	0.07 [-0.02, 0.16], 0.1249		-0.05 [-0.17, 0.07], 0.4168		0.02 [-0.06, 0.09], 0.6760	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Acute Renal Failure						
Interaction p-value	0.6507		0.7943		0.5112	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	1/35 (2.9)	0/59 (0.0)	0/30 (0.0)	2/117 (1.7)	1/65 (1.5)
RR [95%-CI]; p-value	1.21 [0.11, 12.83], 0.8761		NA		1.11 [0.10, 12.02], 0.9309	
OR [95%-CI]; p-value	1.21 [0.11, 13.90], 0.8758		NA		1.11 [0.10, 12.52], 0.9308	
RD [95%-CI]; p-value	0.01 [-0.07, 0.08], 0.8730		NA		0.00 [-0.04, 0.04], 0.9298	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	3/57 (5.3)	0/27 (0.0)	1/60 (1.7)	0/30 (0.0)	4/117 (3.4)	0/57 (0.0)
RR [95%-CI]; p-value	2.89 [0.15, 55.81], 0.4814		1.02 [0.04, 29.46], 0.9923		3.93 [0.21, 73.11], 0.3586	
OR [95%-CI]; p-value	3.00 [0.15, 62.05], 0.4565		1.02 [0.03, 31.18], 0.9923		4.04 [0.21, 77.65], 0.3180	
RD [95%-CI]; p-value	0.03 [-0.04, 0.11], 0.3775		0.00 [-0.06, 0.06], 0.9923		0.03 [-0.02, 0.07], 0.2201	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any SMQ of Cardiac Failure						
Interaction p-value	0.9825		0.4613		0.5759	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	5/58 (8.6)	5/35 (14.3)	7/59 (11.9)	3/30 (10.0)	12/117 (10.3)	8/65 (12.3)
RR [95%-CI]; p-value	0.60 [0.19, 1.94], 0.3960		1.19 [0.33, 4.26], 0.7934		0.83 [0.36, 1.93], 0.6711	
OR [95%-CI]; p-value	0.57 [0.15, 2.11], 0.3929		1.21 [0.29, 5.06], 0.7923		0.81 [0.31, 2.11], 0.6716	
RD [95%-CI]; p-value	-0.06 [-0.19, 0.08], 0.4163		0.02 [-0.12, 0.15], 0.7873		-0.02 [-0.12, 0.08], 0.6784	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	4/27 (14.8)	2/60 (3.3)	2/30 (6.7)	7/117 (6.0)	6/57 (10.5)
RR [95%-CI]; p-value	0.59 [0.17, 2.03], 0.4046		0.50 [0.07, 3.38], 0.4770		0.57 [0.20, 1.61], 0.2886	
OR [95%-CI]; p-value	0.55 [0.14, 2.25], 0.4030		0.48 [0.06, 3.61], 0.4695		0.54 [0.17, 1.69], 0.2847	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4383		-0.03 [-0.13, 0.07], 0.5142		-0.05 [-0.14, 0.05], 0.3252	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Severe SMQ of Cardiac Failure						
Interaction p-value	0.7205		0.3614		0.2529	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	1/58 (1.7)	0/35 (0.0)	2/59 (3.4)	0/30 (0.0)	3/117 (2.6)	0/65 (0.0)
RR [95%-CI]; p-value	1.22 [0.04, 35.56], 0.9063		2.07 [0.10, 44.46], 0.6426		3.36 [0.17, 66.04], 0.4253	
OR [95%-CI]; p-value	1.23 [0.04, 37.57], 0.9061		2.11 [0.09, 48.17], 0.6338		3.42 [0.17, 69.36], 0.3949	
RD [95%-CI]; p-value	0.00 [-0.05, 0.05], 0.9039		0.02 [-0.05, 0.08], 0.5949		0.02 [-0.02, 0.05], 0.3210	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	0/57 (0.0)	0/27 (0.0)	0/60 (0.0)	1/30 (3.3)	0/117 (0.0)	1/57 (1.8)
RR [95%-CI]; p-value	NA		0.25 [0.01, 7.18], 0.4168		0.24 [0.01, 7.12], 0.4114	
OR [95%-CI]; p-value	NA		0.24 [0.01, 7.41], 0.3792		0.24 [0.01, 7.24], 0.3725	
RD [95%-CI]; p-value	NA		-0.03 [-0.09, 0.04], 0.4710		-0.01 [-0.05, 0.02], 0.4701	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any non-Severe SMQ of Cardiac Failure						
Interaction p-value	0.8194		0.5485		0.7735	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	4/58 (6.9)	5/35 (14.3)	6/59 (10.2)	3/30 (10.0)	10/117 (8.5)	8/65 (12.3)
RR [95%-CI]; p-value	0.48 [0.14, 1.68], 0.2520		1.02 [0.27, 3.79], 0.9800		0.69 [0.29, 1.67], 0.4161	
OR [95%-CI]; p-value	0.44 [0.11, 1.78], 0.2429		1.02 [0.24, 4.39], 0.9800		0.67 [0.25, 1.78], 0.4155	
RD [95%-CI]; p-value	-0.07 [-0.21, 0.06], 0.2762		0.00 [-0.13, 0.13], 0.9799		-0.04 [-0.13, 0.06], 0.4358	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	5/57 (8.8)	4/27 (14.8)	2/60 (3.3)	2/30 (6.7)	7/117 (6.0)	6/57 (10.5)
RR [95%-CI]; p-value	0.59 [0.17, 2.03], 0.4046		0.50 [0.07, 3.38], 0.4770		0.57 [0.20, 1.61], 0.2886	
OR [95%-CI]; p-value	0.55 [0.14, 2.25], 0.4030		0.48 [0.06, 3.61], 0.4695		0.54 [0.17, 1.69], 0.2847	
RD [95%-CI]; p-value	-0.06 [-0.21, 0.09], 0.4383		-0.03 [-0.13, 0.07], 0.5142		-0.05 [-0.14, 0.05], 0.3252	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.7.s9.pp
Overall Summary of Standardised MedDRA Queries (SMQs) of Special Interest
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any Serious SMQ of Cardiac Failure						
Interaction p-value	0.9144		0.2694		0.3601	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	2/58 (3.4)	0/35 (0.0)	3/59 (5.1)	0/30 (0.0)	5/117 (4.3)	0/65 (0.0)
RR [95%-CI]; p-value	2.45 [0.11, 52.78], 0.5677		3.10 [0.16, 59.97], 0.4538		5.60 [0.31, 100.86], 0.2430	
OR [95%-CI]; p-value	2.50 [0.11, 57.05], 0.5529		3.21 [0.16, 66.30], 0.4255		5.80 [0.31, 107.94], 0.1834	
RD [95%-CI]; p-value	0.02 [-0.04, 0.08], 0.5115		0.03 [-0.04, 0.11], 0.3478		0.04 [-0.01, 0.08], 0.1037	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	2/57 (3.5)	0/27 (0.0)	0/60 (0.0)	1/30 (3.3)	2/117 (1.7)	1/57 (1.8)
RR [95%-CI]; p-value	1.93 [0.09, 41.38], 0.6742		0.25 [0.01, 7.18], 0.4168		0.97 [0.09, 10.52], 0.9829	
OR [95%-CI]; p-value	1.96 [0.09, 45.05], 0.6674		0.24 [0.01, 7.41], 0.3792		0.97 [0.09, 10.97], 0.9829	
RD [95%-CI]; p-value	0.02 [-0.05, 0.09], 0.6316		-0.03 [-0.09, 0.04], 0.4710		-0.00 [-0.04, 0.04], 0.9830	

Abbreviations: CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; MedDRA: Medical Dictionary for Regulatory Activities; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk; SMQ: Standardised MedDRA Queries (SMQs). SMQ of acute renal failure includes any preferred term which contains Azotaemia, Blood creatinine increased, Proteinuria, Renal failure or Renal impairment; SMQ of cardiac failure includes any preferred terms which contains Acute pulmonary oedema, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomegaly, Oedema, Oedema peripheral, Orthopnoea or Pulmonary oedema.
In AE severity analysis, a subject is only counted once with the maximum severity.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_7_m_pt_smq_bl25d_pp.sas using SAS 9.4

Table 12.4.4.1.6.s9.pp
Overall Summary of Adverse Drug Reactions (ADR)
PP Population
Subgroup: 1.Baseline 25D< 20 ng/mL vs 2.Baseline 25D ≥ 20 ng/mL

	CL-3001		CL-3002		Meta-Analysis	
	ER-Calcifediol (N=115)	Placebo (N=62)	ER-Calcifediol (N=119)	Placebo (N=60)	ER-Calcifediol (N=234)	Placebo (N=122)
Number of Patients with Any ADR						
Interaction p-value	0.8413		0.8340		0.6374	
1.Baseline 25D < 20 ng/mL	N1=58	N1=35	N1=59	N1=30	N1=117	N1=65
n/N1 (%)	8/58 (13.8)	9/35 (25.7)	14/59 (23.7)	4/30 (13.3)	22/117 (18.8)	13/65 (20.0)
RR [95%-CI]; p-value	0.54 [0.23, 1.26], 0.1533		1.78 [0.64, 4.94], 0.2683		0.94 [0.51, 1.74], 0.8441	
OR [95%-CI]; p-value	0.46 [0.16, 1.34], 0.1496		2.02 [0.60, 6.79], 0.2484		0.93 [0.43, 1.99], 0.8444	
RD [95%-CI]; p-value	-0.12 [-0.29, 0.05], 0.1689		0.10 [-0.06, 0.27], 0.2114		-0.01 [-0.13, 0.11], 0.8454	
2.Baseline 25D≥ 20 ng/mL	N2=57	N2=27	N2=60	N2=30	N2=117	N2=57
n/N2 (%)	8/57 (14.0)	8/27 (29.6)	9/60 (15.0)	3/30 (10.0)	17/117 (14.5)	11/57 (19.3)
RR [95%-CI]; p-value	0.47 [0.20, 1.13], 0.0910		1.50 [0.44, 5.14], 0.5185		0.75 [0.38, 1.50], 0.4196	
OR [95%-CI]; p-value	0.39 [0.13, 1.18], 0.0892		1.59 [0.40, 6.36], 0.5107		0.71 [0.31, 1.64], 0.4218	
RD [95%-CI]; p-value	-0.16 [-0.35, 0.04], 0.1159		0.05 [-0.09, 0.19], 0.4849		-0.05 [-0.17, 0.07], 0.4388	

Abbreviations: ADR: Adverse Drug Reaction; CI: Confidence Interval; ER: Extended Release; PP: Per-Protocol; OR: Odds Ratio; PT: Preferred Term; RD: Risk Difference; RR: Relative Risk.
ADR includes any preferred term which contains Blood calcium increased, Hypercalcaemia, Blood phosphorus increased, Hyperphosphataemia, Constipation, Nausea, Diarrhoea, Abdominal discomfort, Abdominal pain upper, Dry mouth, Vomiting, Asthenia, Dizziness, Dizziness postural or Headache.
Statistical methods: The meta-analysis was conducted by pooled individual patient data without adjustment. If there is no event in one treatment group, 0.5 is added for calculation. The 95% CI is calculated by the Wald method. The subgroup interaction p-value is calculated from InRR using the fixed-effect model. Estimates of Relative Risk<1, Odds Ratio<1 and Risk Difference<0 are in favor of ER-Calcifediol.
25 D: 25-Hydroxyvitamin D.
Source: Listing 14.6.1
Note: Adverse Events were coded using MedDRA Dictionary version 15.0 or higher. TEAEs are defined as all AEs, regardless of relationship to Study Drug, which occur during or after treatment.
N (%): Percentage is based on randomized sample size as denominator. Subjects are counted only once for each SOC and Preferred Term.
S:/Departmental Shares/R&D/BIOMETRICS/Relypsa/BioStat/$Biometric/rayaldee_opko/amnog_b/pgm/s9_bl25d_pp/T12_4_4_1_6_m_pt_adr_bl25d_pp.sas using SAS 9.4